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(Concluded)

HYDATIDIFORM MOLE—A PATHOLOGICO-CLINICAL CORRELATION OF 200 CASES*†

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IT IS the purpose of this paper to determine what, if any, correlation there exists between the histologic appearance of a hydatidiform mole and the subsequent clinical course of the patient with respect to the development of chorionic malignancy. Because of the lack of any universally recognized histologic criteria, which invariably separate the malignant from the benign moles, it has been stated by some pathologists[1, 10, 15, 16, 18, 21] that such criteria do not exist. Other authors,[14, 22] however, state that such criteria do exist and can be correlated with the patient's clinical course.

In going over the literature from 1937 (when Mathieu[11, 12] reviewed it) up until the present time, it is evident that no systematic attempt has ever been made to correlate pathologically a series of moles with their clinical outcome. To accomplish this correlation it was decided in 1935, when one of us (A.T.H.) was Assistant Pathologist of the Boston Lying-in Hospital, to collect from various obstetric clinics, general hospitals, and other interested contributors, a large enough series to determine whether such a correlation exists. This study has gone on since that time, although the 200 cases in this report were collected from January, 1932, to January, 1942—a period of approximately eleven years.

Material and Methods

The source of this material is from 109 medical communities in the eastern half of the United States. To all of the many contributors, we are individually and collectively grateful, for without their help it would have been mani-

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festly impossible to carry out this study. To Dr. F. C. Irving we are indebted for encouragement and help in placing the series from the Boston Lying-in Hospital at our disposal. To Drs. S. B. Wolbach, Shields Warren, Olive Gates, and Frederick Parker, Jr., we are indebted for advice and diagnostic help. Misses Carmen Atwell and Ruth Dacey have materially assisted with this study by their secretarial help in keeping the records of these patients up to date. Dr. Florence C. Slater has aided greatly by helping to review the literature from 1942 to the present time.

In order to make this study as objective as possible, every case was studied independently by each of us. If a disagreement in the histologic grading of the mole was encountered, we rationalized our differences of opinion before either of us became aware of the patient's clinical course. Some of the cases, such as those from our own clinic, were sent to us for a pathologic opinion, so that in such instances the clinical outcome was not yet known. In reviewing old cases, on whom clinical data were available, the latter was not recorded on the master sheet for each case until our final diagnosis had been made. In the rare case whose identity one of us recognized, either by its particular histology, shape of the section, or pathologic number, it was fortunate that the other observer failed to recognize the identity of the specimen; and, hence, the objectivity of the grading was preserved. In some instances, we had both the molar tissue as well as uterine curettings. If the former showed a lower histologic grading than the latter, or vice versa, the grading of the mole became the final diagnosis. In this way the study became a more objective correlation between the mole per se and its clinical course. In actual practice, of course, the pathologist should and does make his final report on all the available evidence.

During the course of the study, it became evident that some histologic criteria had more significance with respect to malignancy than did others. We naturally used such information in grading subsequent moles. Also, in going back over previously graded moles, whose identity purposely remained anonymous, we applied these progressively learned criteria to the earlier cases so as to make all grading uniform. It seemed unfair to us, as well as unobjective, finally to misgrade an early mole in the series merely because of ignorance of the significance of a particular histologic pattern.

The question naturally arises as to whether such results from a series of 200 moles are statistically significant.* The number of cases in this study was not chosen on the basis of statistical validity, although it was hoped to get as large and significant a series as possible. Since the average incidence of hydatidiform mole is one in approximately 2,000 deliveries (1:2,051 for the 14 Boston Lying-in cases from the Ward Service), these cases represent, on an average, the moles from 400,000 pregnancies, or about one-seventh of all the deliveries in the United States during 1945.

The question of whether these cases represent an adequate random sampling of moles throughout the country is also pertinent.* The middle and northern Atlantic coastal regions are well represented, and a few specimens were obtained from portions of the middle western and southern states east of the Mississippi River. It appears from a review of the literature, in comparison with this series, that all of the major varieties and complications of hydatidiform mole are represented in this material; these include all the grades of ultimate malignancy with their usual prognosis, death from postoperative sepsis, spontaneous perforation of the uterus, and fatal hemorrhage following evacuation of the mole. One of our patients even had three successive hydatidiform moles, all benign. Hence, the data and conclusions appear not only medically sound, but statistically valid.

*Miss Jane Worcester of the Department of Biostatistics, Harvard School of Public Health, has kindly gone over the data of this paper. The material represents an adequate random sample of hydatidiform moles. She feels, furthermore, that it is not necessary to subject the data to statistical analysis since the conclusions are obviously valid.

To be sure, some of these cases have been sent from other clinics as diagnostic problems, but they are in the minority. The vast majority of the outside cases were obtained by contacting persons who had access to such material so that the cases from any clinic, hospital, or locality tend to be a random sample from that region.

Histologic Grading of Hydatidiform Moles

In grading these potentially malignant tumors, two general histopathologic principles were kept in mind: (1) the degree to which the trophoblast resembled or differed from that of normal placental tissue in the first trimester of pregnancy, and (2) the absolute degree to which it appeared to be undifferentiated, using the criteria employed in grading any tumor. Comparison with first trimester trophoblast was used as a criterion, since it is from pathologic chorions of this general developmental age that hydatidiform moles arise. (For details of the genesis of these structures see Hertig and Edmonds.[4] As the study progressed, it became clear that the more malignant the mole, the more its trophoblast resembled the differentiating trophoblast of the early human ovum during its first week after implantation. Histologic details of such early ova are found in the papers of Hertig and Rock,[5, 6] and Heuser, Rock, and Hertig.[9]

The usual morphologic criteria of malignancy, such as pleomorphism, degree of cellular differentiation, abnormal rate of growth, loss of basement membrane, invasion of stroma, and vascular invasion (universally observed by pathologists in grading all tumors) were also used. These principles were employed, since it was assumed that actual malignancies must follow the general rules of tumor growth, invasion, and metastasis. However, it is evident from a study of placental development and growth that a tumor derived from trophoblast differs from any other tumor in two fundamental respects: (1) it is derived from structures that are not an integral part of the host, and (2) its benign prototype is normally invasive, opens and permeates blood vessels, and thereby often metastasizes to the lungs.

Because of the first fundamental difference, namely, the tumor host relationship, it is theoretically possible (and actually quite probable) that no matter how malignant a mole appears microscopically, any particular area of trophoblast may not have been in juxtaposition to the uterine wall, and hence could not have invaded it. This probably explains the lack of any absolute clinico-pathologic correlation which plagues all pathologists who attempt to grade an individual hydatidiform mole. Furthermore, since a mole is often a bulky structure and has been shown to vary in microscopic appearance from portion to portion, it is imperative to select at least five, and preferably ten, regions for routine study. Particular attention should be paid to curettings, for they offer the best possibility of evaluating a mole. Too often the clinician has carefully saved the mole and borne it proudly to the pathologic laboratory, having discarded the curettings as being inconsequential to the diagnosis.

The second fundamental difference, namely, the semimalignant attributes of all trophoblast, makes it clear that, since most pregnant patients have trophoblastic metastases, but rarely die from chorionepithelioma, there must be some factor other than its pure morphologic appearance which allows one metastasis to persist and kill the patient, while the other disappears. The lytic substance postulated by Fraenkel[3] is possibly the explanation for this phenomenon.

With all these difficulties in mind, it is still possible to correlate in a general fashion the malignant potential of a hydatidiform mole with the clinical outcome of the patient. This becomes apparent in a large series, as shown in Table I, although not always so evident in any individual case. Fig. 1 is a

graphic representation of the percentage distribution of the various molar groups in the series. It is evident that the largest group (29.5 per cent) of the cases are classified as possibly malignant (Group IV), although only 17 per cent of this group showed ultimate malignancy of some degree or other (Fig. 2). This single fact emphasizes what all pathologists and clinicians have suspected, namely, that many moles may look fairly malignant, but few actually become so. Fig. 2 summarizes the distribution of the various grades of chorionic malignancies according to the molar group into which they were originally placed. Thus, for example, only 10 of the 59 possibly malignant moles (Group IV) actually realized their malignant potentiality, even though all looked more or less alike as original moles. It must be emphasized further that the various grades of chorionic malignancy vary widely in ultimate clinical prognosis, irrespective of their original molar grouping. This will be dis-

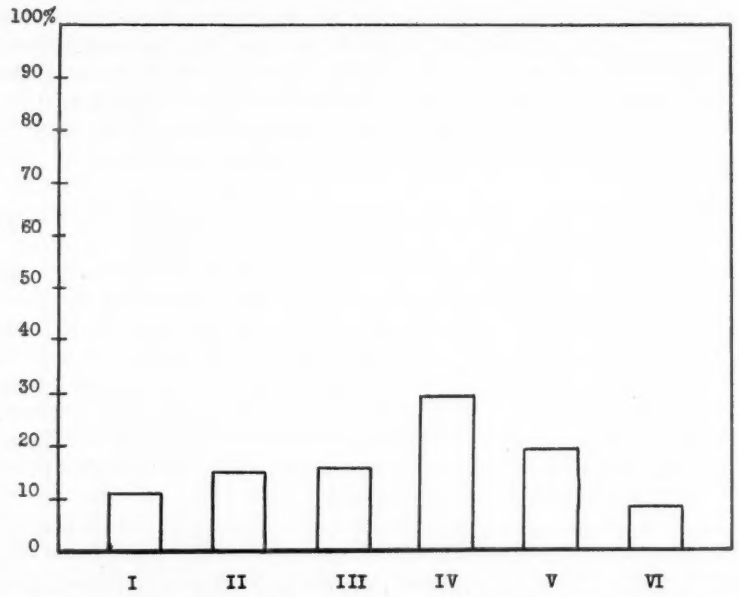

Fig. 1.—Distribution of molar groups in 200 cases of hydatidiform mole.

cussed more in detail later. Fig. 3 graphically represents the percentage distribution of the clinically malignant varieties of chorionepithelioma according to their original molar grouping. By comparing Figs. 2 and 3, it becomes apparent that there is still a correlation between the original grouping of a mole, irrespective of whether one includes all grades of chorionic malignancy (Fig. 2) or only the clinically malignant chorionadenoma destruens and choriocarcinoma (Fig. 3). In spite of the lack of specific clinico-pathologic correlation in any given mole, the information gained from this study has enabled the authors to evaluate the malignant potentiality of an individual mole much more accurately than before the study was undertaken.

I. Benign Hydatidiform Moles

(None to slight hyperplasia of trophoblast)

In this group there were 22 specimens, none of which showed either pathologic or clinical evidence of malignancy. Adequate follow-up data are available for this group, as summarized in Table III. The details of such prognostic data will be reserved for discussion later on in the paper.

None of these moles show a significant departure from the normal trophoblast pattern of immature chorionic villi. The villous stroma, as of all moles, has been converted into a cystic mass at the periphery of which is a layer of loose, avascular, fibroblastic, or mesoblastic tissue. The trophoblast of some villi still possesses a normal double-layered epithelium of the classic pattern. Many villi, however, show mechanical thinning and distortion of their epithelial covering, presumably due to stretching incident to hydropic swelling of the villus. In occasional areas of nearly every mole of this group is slight benign proliferation of syncytium and/or Langhans epithelium, as shown in

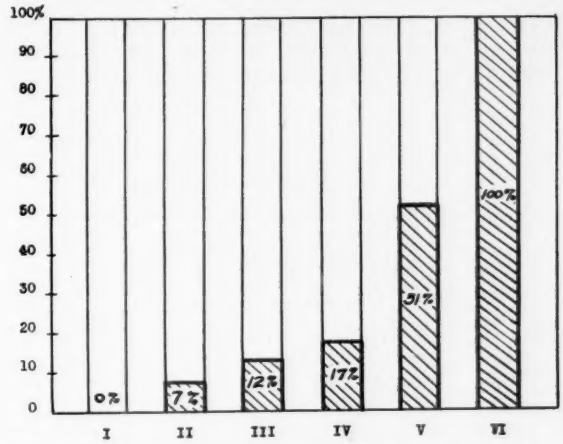

Fig. 2.—Distribution of all grades of chorionic malignancies by molar groups in 200 cases of hydatidiform mole.

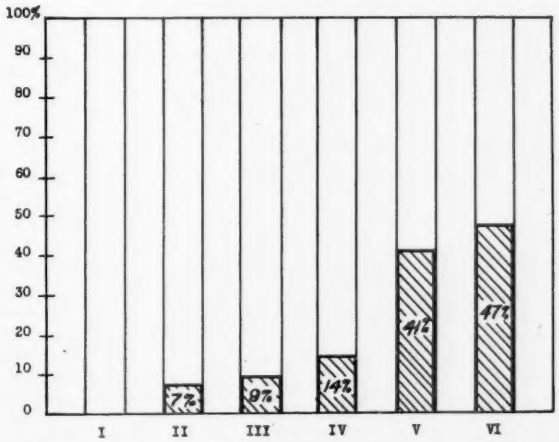

Fig. 3.—Distribution of chorionic malignancies by molar groups (including only chorionadenoma destruens and chorioncarcinoma) in 200 cases of hydatidiform mole.

Fig. 4,*A*. The relative proportion of these proliferative epithelial elements is by no means constant, either from field to field in the same mole or in the group as a whole. The Langhans epithelium and its associated trophoblastic masses, comparable to cell columns of the normal villi, are often the seat of "fibrinoid" degeneration. This is a normal occurrence in aging trophoblast, as pointed out by Wislocki and Bennett.[23] Mitoses in the Langhans epithelium are no more frequent, indeed appear less so, than in the normal immature villi of six to twelve weeks. Mitoses never occur in syncytium, in our experience, either in early ova, developing placentas, or hydatidiform moles.

TABLE I. HYDATIDIFORM MOLE CLASSIFICATION

GROUP	NAME	HISTOLOGIC CRITERIA	NO. CASES	NO. MALIGNANCIES
I	Benign	None to slight hyperplasia of trophoblast	22	0
II	Probable benign	Slight to moderate hyperplasia	30	2
III	Possible benign	Hyperplasia with slight anaplasia	33	4
IV	Possible malignant	Moderate anaplasia with hyperplasia	59	10
V	Probable malignant	Marked anaplasia with hyperplasia	39	20
VI	Malignant	Exuberant trophoblastic growth (variable mitotic activity) with marked anaplasia, and often evidence of endometrial invasion	17	17
		Totals	200	53

TABLE II. GRADES OF 53 CHORIONIC MALIGNANCIES DISTRIBUTED ACCORDING TO MOLAR GROUPS IN 200 CASES OF HYDATIDIFORM MOLE

	I	II	III	IV	V	VI	TOTAL CASES	PER CENT
Chorionepithelioma in situ	0			1	1	5	7	3.5
Syncytial endometritis	0		1	1	3	4	9	4.5
Chorionadenoma destruens	0	2	3	8	13	6	32	16.0
Chorioncarcinoma	0				3	2	5	2.5
Total	0	2	4	10	20	17	53	26.5

TABLE III. FOLLOW-UP DATA ON CLINICALLY BENIGN MOLES

ORIG. GROUP	CASES	SUBSEQUENT PREGNANCY	ALIVE AND WELL TWO (+) YEARS	ALIVE AND WELL TWO (−) YEARS	NO DATA	REMARKS
I	22	12	5	5	0	
II	28	13	9	2*	4	*One with negative uterus on hysterectomy and one with negative curettings from uterus.
III	29	15	8	5†	1	†Three with negative A-Z tests, 2 to 7 months. One with negative uterus after hysterectomy.
IV	49	23	11	11‡	4§	‡Two negative hysterectomies and four negative curettings from uterus. §One died of shock—no autopsy.
V	19	10	3	4	2	
Totals	147	73	36	27	11	92.5% Follow-up

II. Probably Benign Hydatidiform Moles

(Slight to moderate hyperplasia of trophoblast)

In this group (Figs. 4,*B* and 5) there were 30 cases, two of whom showed clinical evidence of low grade chorionic malignancy (Table II) of the type characterized as chorionadenoma destruens. Both are alive and well following hys-

terectomy, three and ten years, respectively. Of the remaining 28, only four have insufficient follow-up data, the other 24 being alive and well, with 13 having subsequently become pregnant. Details of these prognostic data are summarized in Table III.

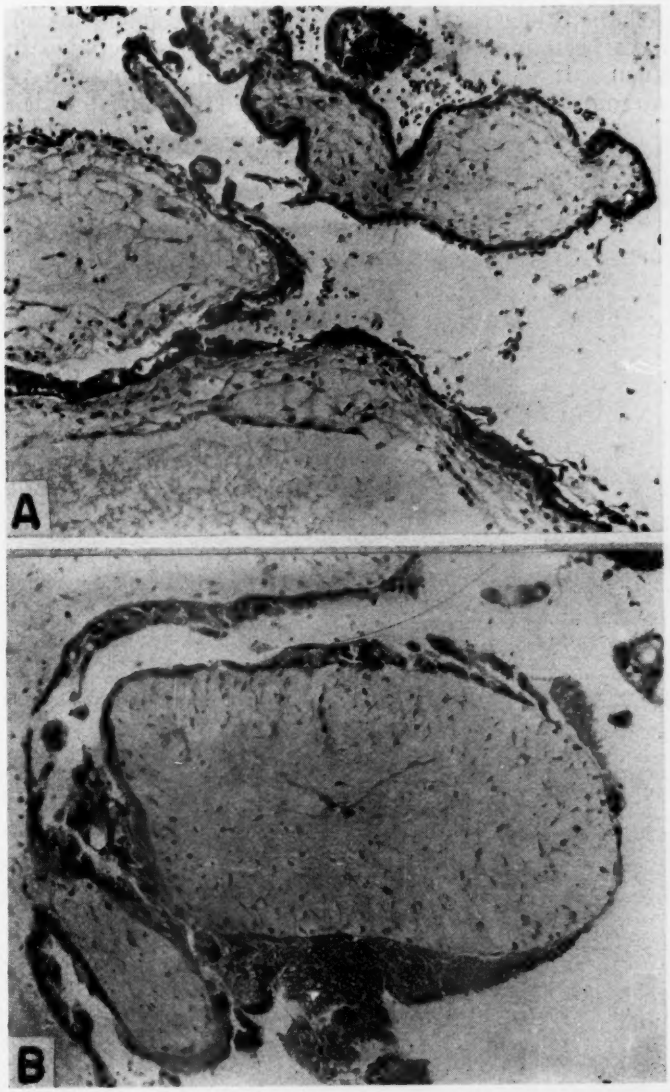

Fig. 4.—*A.*, A benign hydatidiform mole (I) showing portions of three villi in varying stages of hydatid degeneration. The trophoblast is normal or at most only slight hyperplasia. Patient was living and well eleven years later. (M-2, ×110.)

B., A probably benign hydatidiform mole (II) showing moderate trophoblastic hyperplasia, confined mostly to the syncytium. Patient had a baby five years later. (M-52, ×110.)

These moles as a group are characterized by slight to moderate hyperplasia of both trophoblastic elements, but no essential evidence of anaplasia. In grading all tumors, there is no sharp line of demarcation between each designated grade. This situation is also true with regard to hydatidiform moles. This group, therefore, represents a gradual transition from the obviously benign moles of Group I, with little, if any, hyperplasia and a good

deal of benign degeneration, to the more disturbing moles of Group III with much hyperplasia and beginning but significant anaplasia. There is some variation in the different specimens of this group, as can be seen by the three examples depicted in Figs. 4,*B* and 5. There is no evidence of malignant change in the trophoblast of either of these specimens, although the one in Fig. 5 subsequently invaded the uterus. In reappraising this specimen, we felt that it probably should have been placed in Group III, but it is included in Group II as originally graded. It is noteworthy that the villi which were penetrating the uterus were surrounded by a well-differentiated trophoblast which recapitulates

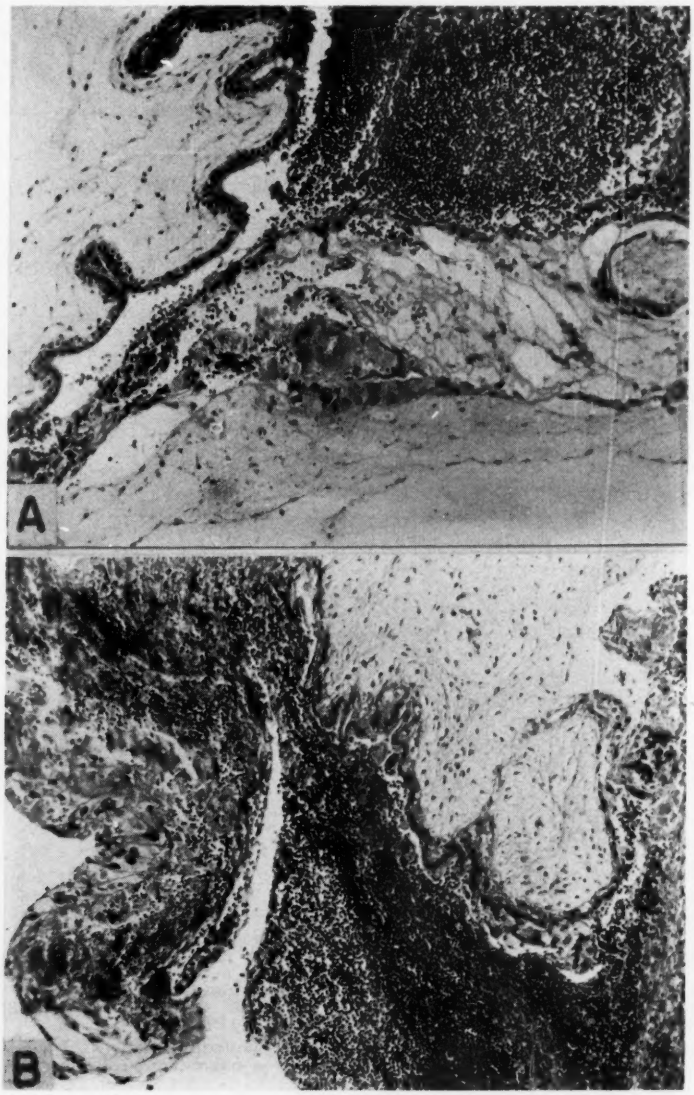

Fig. 5.—*A.*, A probably benign hydatidiform mole (II) showing normal trophoblast on the upper left villus and hyperplastic epithelium on the lower one, the Langhans element of which is slightly anaplastic and the syncytium vacuolated. Patient developed a low grade chorionadenoma destruens, but was well three years later. This mole, in retrospect, perhaps should have been graded higher as possibly benign (III). (M-200, ×110.)

B., Same case as above to show fibrinoid degeneration of previously hyperplastic trophoblast toward left. (M-200, ×110.)

that of the twelve-day ovum,[5] a stage just prior to the formation of the chorionic villi. It is also of interest that the patient is alive and well three years after the hysterectomy, the latter having been done for a persistently positive Friedman test two and four weeks after the passage of the mole.

This group can, therefore, be summarized as one in which the ever-present threat of chorionic malignancy following hydatidiform mole is just beginning to manifest itself, even though the specimens as a group show little of a disturbing nature in their trophoblast.

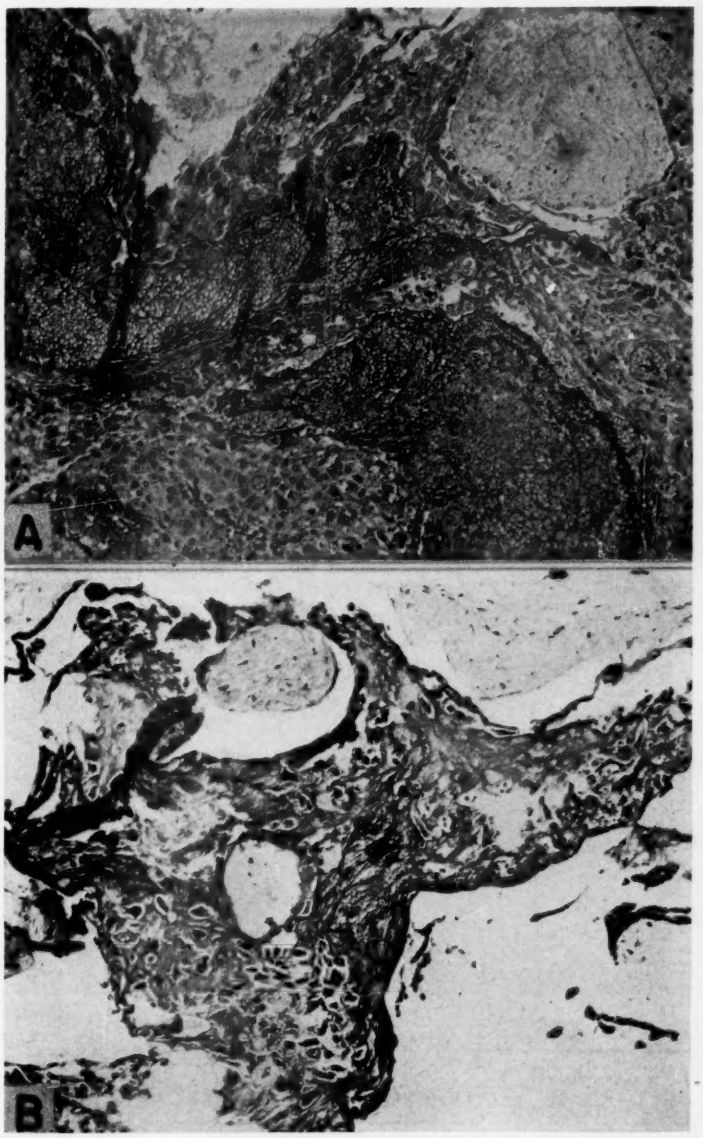

Fig. 6.—*A.*, A possibly benign hydatidiform mole (III) with moderate hyperplasia of cytotrophoblast (lower left) and slight anaplasia (upper left). Patient became pregnant fifteen months later, but miscarried. (M-8, ×110.)

B., A possibly benign hydatidiform mole (III) with persisting anaplasia within degenerated trophoblast. Patient developed a low grade chorionadenoma destruens, but was well eight years and eight months later. (M-37, ×110.)

III. Possibly Benign Hydatidiform Moles

(Hyperplasia with slight anaplasia of trophoblast)

In this group (Fig. 6) there were 33 cases, of whom four showed clinical evidence of low grade malignancy, the types of which are seen in Table II. Of the four malignancies, one was a syncytial endometritis and three were of chorionadenoma destruens type. The former patient died on the seventh postoperative day of peritonitis, while the other three are living and well two months, two years, and 4 years, respectively. The follow-up data on the chorionic malignancies as a group are shown in Table IV. Of the 29 remaining in this group which were clinically benign, only one has no follow-up data, the other 28 being alive and well, with 15 of them having become pregnant. Details of these prognostic data are summarized in Table III.

TABLE IV. FOLLOW-UP DATA ON CHORIONIC MALIGNANCIES

GRADE	CASES	SUBSEQUENT PREGNANT	LIVING AND WELL		NO DATA	DIED	PER CENT CURED	REMARKS
			$\bar{C}$ UTERUS	$\bar{S}$ UTERUS				
Chorion-epithelioma in situ	7	2	2*	3†	0	0	100	*Living and well; 4 to 5½ years †Two cases living and well; 3 plus years, and remaining one had negative uterus and was living and well 1½ years postoperatively
Syncytial endometritis	9	0	2*	6†	0	1‡	89	*Living and well 7 months and 4 years, respectively †3 cases living and well 3 to 10 months; 3 cases living and well 4 to 9 years ‡Died of sepsis, 7 days postoperatively (hysterectomy)
Chorion-adenoma destruens	32	0	0	27*	4	1†	97	*Living and well 1 to 14 years postoperatively (25 cases, 2 or more years) †Died 5 days postoperatively (hysterectomy) of sepsis
Chorion-carcinoma	5					5*	0	*Four patients died with uterus still in, the fifth not being removed until just before death
Totals	53	2	4	36	4	7	86.6	89% follow-up, excluding 2 postoperative deaths

The moles in this group are characterized by variable amounts of hyperplasia of both trophoblastic elements, together with slight but definite anaplasia, examples of which are seen in Fig. 6. Of the two examples chosen, the one in Fig. 6, *A* is at first glance more disturbing than the one in Fig. 6, *B*. However, there is only very slight anaplasia in the former, whereas this feature is more

prominent in the latter. It may be of significance that Fig. 6, *A* represents an ultimately benign mole clinically, whereas Fig. 6, *B* is from a mole that showed evidence of uterine invasion by a relatively well-differentiated trophoblast.

Another malignant mole in this group, the twenty-fifth mole examined by one of us (A. T. H.) up to that time, showed a tissue-culture-like growth of both syncytio- and cytotrophoblast upon the surface of blood clot as seen in

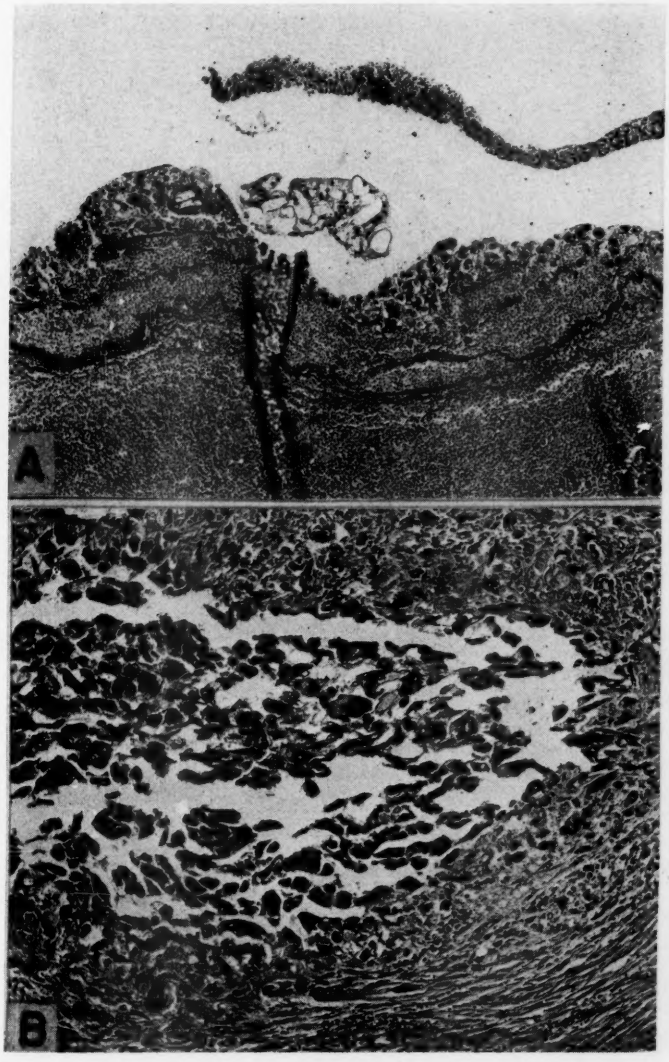

Fig. 7.—*A.*, Tissue-culture-like growth of both trophoblastic elements upon the surface of blood clot. The original mole was possibly benign (III). Patient developed chorionadenoma destruens as shown in Fig. 7, *B*. (M-21, ×50.)

B., Uterus showing locally invasive anaplastic trophoblast within myometrium of same case as Fig. 7, *A*. Patient was well two years postoperatively. (M-21, ×125.)

Fig. 7, *A*. The mole itself, otherwise, resembled the rest of the group. Since this was the first time in the series such a histologic pattern had been encountered, it was misinterpreted, although the clinician was warned about the potential danger in view of our inability to interpret definitely this finding. Hysterectomy was performed forty-five days after the passage of the mole because of a positive A-Z test performed on the fortieth day. Evidence of clin-

ical subinvolution of the uterus and vaginal bleeding were also present. It is of interest that the uterus showed a relatively undifferentiated nest of tumor within the myometrium, as shown in Fig. 7, *B*. These invading trophoblastic cells resemble those of the 7- to 8-day ovum[7] just after implantation. Most of them are cytotrophoblastic in type, but the larger ones are young syncytiotrophoblastic cells. The patient was alive and well two years postoperatively.

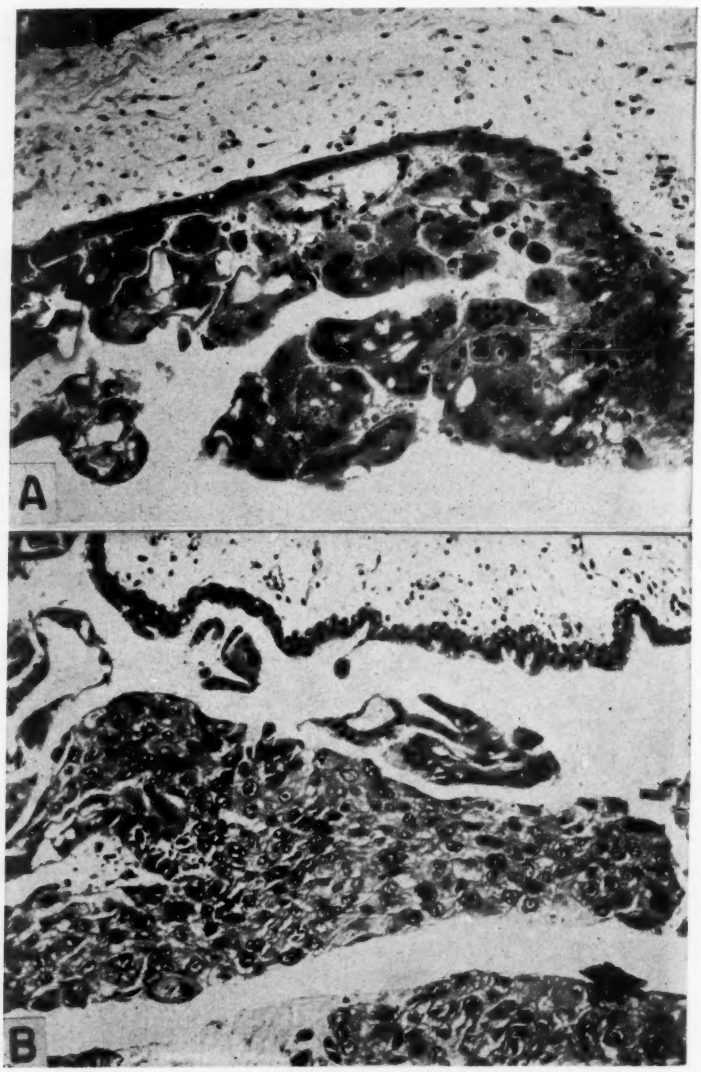

Fig. 8.—*A.*, A possibly malignant hydatidiform mole (IV) showing marked syncytiotrophoblastic proliferation with slight anaplasia. Same case as Fig. 8, *B*. (M-88, ×150.)

B., Same case as Fig. 8, *A*, but showing marked cytotrophoblastic hyperplasia with moderate anaplasia. Patient was well six and one-half years after passage of mole. (M-88, ×150.)

This group can, therefore, be summarized as one in which the trophoblast is more abundant and somewhat less differentiated than in the previous groups, features which are reflected in the increasing percentage of ultimate, although low grade malignancy. Also, one encounters for the first time evidence of trophoblastic growth independent of the villi, a feature often associated with ultimate malignancy.

IV. Possibly Malignant Hydatidiform Moles

(Variable hyperplasia and moderate anaplasia of trophoblast)

There were 59 cases in this group with 10 malignancies whose grades are shown in Table II. Most of these (eight) were of chorionadenoma destruens type, with one each of syncytial endometritis and chorionepithelioma in situ.

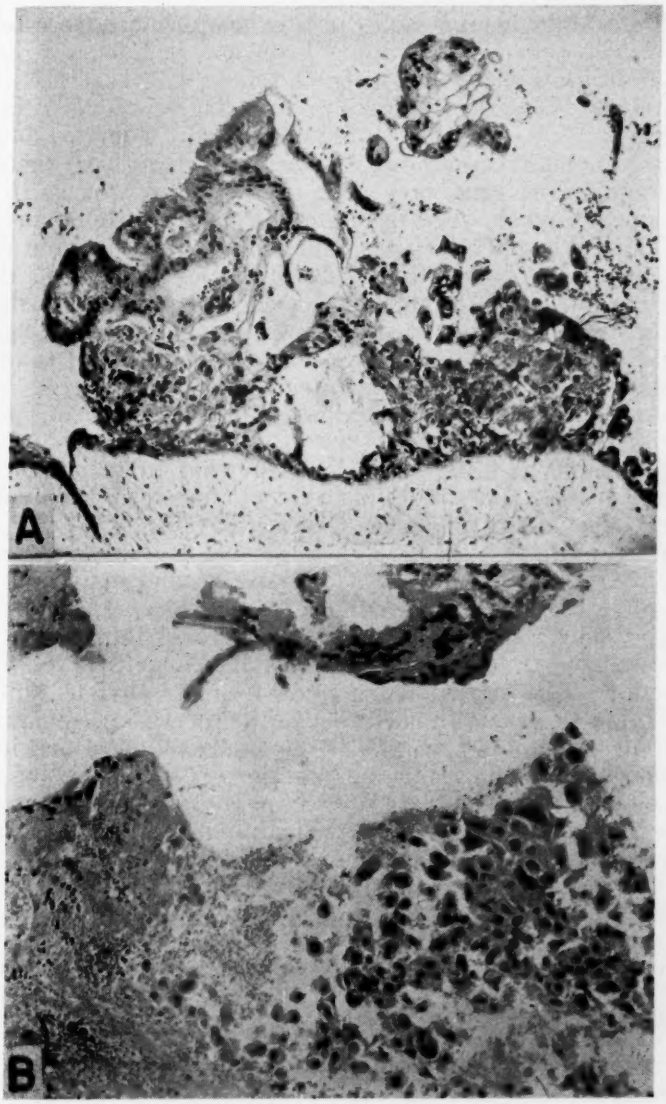

Fig. 9.—*A.*, A possibly malignant hydatidiform mole (IV) with moderate hyperplasia and slight anaplasia of both trophoblastic elements. Same case as Fig. 9, *A*. Patient developed a low grade chorionadenoma destruens, but was well five years postoperatively. (M-40, ×110.)

B. Same as Fig. 9, *A*, but showing moderate anaplasia of cytotrophoblast. This is the most malignant area in the entire mole. (M-40, ×125.)

The patient with syncytial endometritis was alive and well ten months later, while the one with chorionepithelioma in situ was normally pregnant (verified by x-ray) seven months later. Of the 8 cases of chorionadenoma destruens, one died postoperatively of peritonitis, one had no follow-up, while the re-

maining six are living and well from sixteen months (one patient) to eleven years (five from five to eleven years). The patient well five years later had multiple negative Friedman tests postoperatively. It is of interest to note that this patient's uterus showed extension of the low grade tumor process to the surface of the uterus beneath the bladder flap, showing the locally malignant character of this tumor. The general follow-up data on all the chorionic malignancies are summarized in Table IV.

Of the 49 clinically benign moles in this group, there were follow-up data on 45, 23 of which were followed by subsequent pregnancies. The prognostic data in these cases are summarized in Table III.

The significant histologic features of this largest group of moles are seen in Figs. 8 and 9. The abundant growth of both syncytio- and cytotrophoblast is evident in both cases here represented. However, their proportions and exact histologic patterns vary with each mole as well as in various portions of the same specimen. For example, the syncytiotrophoblast in each case depicted is exuberant and relatively benign in appearance, but in Fig. 8 it is much less vacuolated than in Fig. 9. These vacuoles represent the embryonic recapitulation of placental intervillous space formation, and first appear in the developing ovum of eight to nine days of age.[7] It is interpreted as evidence of relative benignity even though, on rare occasions, it is associated with a truly invasive mole of the chorionadenoma destruens type. It has never been seen, to our knowledge, in the invasive and metastasizing portions of the fatal variety of chorioncarcinoma.

The cytotrophoblast likewise varies somewhat in appearance, both cases being rather primitive, and simulating that of the seven-day ovum which normally and actively invades maternal tissues.

The clinically benign case, shown in Fig. 8, possesses, in general, rather more abundant trophoblast than that of the clinically malignant mole in Fig. 9, yet they differ little in their degree of essential anaplasia. However, the malignant case shows some tissue-culture-like growth as seen in Fig. 9, *B*. The ultimately invasive trophoblast is still morphologically less differentiated than any portion of its parent mole, aside from its obvious ability to invade the uterus. These two cases thus epitomize the increasing general activity and anaplasia of the trophoblast in this, as compared to the previous group, an expression of which is the rising percentage (17 per cent) of malignancies. The two specimens also illustrate how impossible it is in any given case of mole to give it a definitely benign or malignant prognosis. This difficulty becomes less in the two remaining groups, as shown in Fig. 2.

V. Probably Malignant Hydatidiform Moles

(Variable hyperplasia and marked anaplasia of trophoblast)

This group of 39 cases contains 20 patients who ultimately developed malignancy of one grade or another, and 19 who remained clinically benign. The grades of subsequent chorionic malignancy are summarized in Table II. It is apparent from the relatively high proportion and variety of malignancies that this is an important and dangerous group of moles. The follow-up data on the benign and malignant group are summarized in Tables III and IV, respectively. The ultimate prognosis on the clinically benign group is excellent, with only two patients of the 19 untraceable; ten of the group subsequently became pregnant. The malignant group also has a good prognosis, except for the three with chorioncarcinoma, all of whom died within two years of the passage of the mole.

The striking thing about this group as a whole, two examples of which are seen in Figs. 10 and 11, is the marked anaplasia. There is often a good

deal of benign hyperplasia as well, although this may be quite variable. The trophoblast tends to be of a single indifferent or primitive variety, rather than being sharply divided into the syncytial and Langhans types. The indifferent trophoblast, such as seen in all the examples here shown, tends to resemble that of the implantation pole of a very recently embedded ovum.

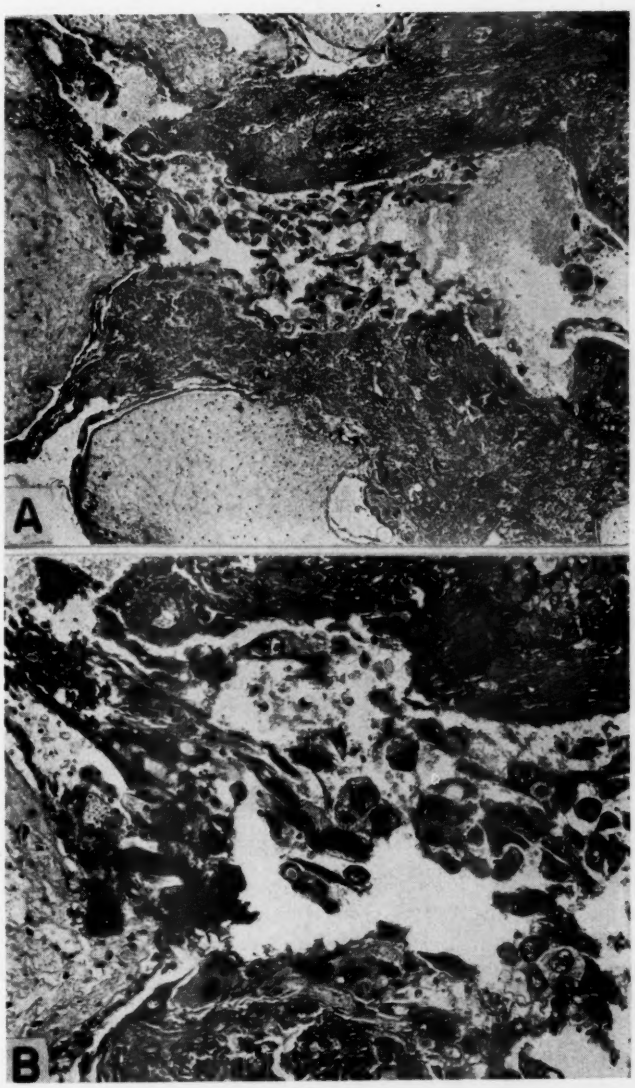

Fig. 10.—*A.*, A probably malignant hydatidiform mole (V) to show highly anaplastic trophoblast amid an area of fibrinoid degenerated trophoblast. Patient was well one and one-half years later. Same case as Fig. 10, *B*. (M-179, ×50.)

B., Higher power detail of same trophoblast shown in Fig. 10, *A*. (M-179, ×150.)

Here the trophoblast is indifferent, or, as we have chosen to call it, "admixed," because the syncytio- and cytotrophoblastic cells have no particular arrangement, and also may differ little from each other in this primitive phase of their development. However, as the early syncytiotrophoblastic cell differentiates, it becomes larger, darker, more irregular, and possesses a hyperchromatic nucleus. The latter, by budding, produces a multinucleated structure which characterizes syncytium throughout the remainder of its life. Fig. 10

shows an excellent example of this anaplastic epithelium that resembles in many details the normal primitive trophoblast of the early implanting ovum. It is interesting that the patient from whom this specimen was received is alive and well one and one-half years after the mole was passed.

Another feature of interest and probable importance in this group is the loss of basement membrane associated with the adjacent anaplastic trophoblast. A more marked degree of this phenomenon is present in cases of trophoblastic invasion of the villous stroma seen in some cases of malignant moles. Reference will be made to this point later. The patient from whom this specimen was obtained developed a chorionadenoma destruens, and came to hysterectomy five days after the passage of the mole. Unfortunately, follow-up data are available on this patient for only four months, after which she failed to return to the hospital. Her local physician was contacted, but his records of twenty-four years ago were not adequate to trace the patient.

The second case illustrating this group (Fig. 11) is not essentially different from any of the others from a morphologic standpoint, although the patient died from chorioncarcinoma within a year after passage of the mole. Only two sections of the mole were available and curettage had been done. Therefore, the uterus had not been removed. It has been noted by various authors[2, 7, 13, 15] that many cases of fatal chorioncarcinoma show little if any tumor in the uterus. The above, at autopsy, did show a single hydatid villus attached to the myometrium by innocuous appearing trophoblast, as seen in Fig. 11, *B*. The degree of trophoblastic anaplasia does not approach that of even an invasive mole, let alone that of a chorioncarcinoma. It appears, therefore, that the metastases which killed the patient gained early entrance to the maternal vascular system during the growth of the mole, although this point is not capable of proof from the data available.

The probably malignant moles, in summary, seem to justify their designation, because all of them appear extremely anaplastic and capable of invading the uterus or metastasizing to distant sites, even though only half of them ultimately do so.

VI. Malignant Hydatidiform Moles

(Exuberant hyperplasia and marked anaplasia of trophoblast, often invading the endometrium)

This small group of 17 cases all showed various degrees of morphologic and/or clinical malignancy. The distribution of these cases among the various grades of chorionic malignancy is shown in Table II. Examples of these various grades, all originally diagnosed as malignant, are seen in Figs. 12 to 21. The prognosis of the patients in this group is good, except for the two cases of fatal chorioncarcinoma, who were dead ten and sixteen months, respectively, after passage of the mole. The general follow-up data on all the various grades of chorionic malignancy are given in Table III.

A. Chorionepithelioma in Situ

(Morphologic malignancy plus endometrial invasion)

Of the seven cases in this general group (Table II), five were originally called malignant and put in Group VI from the examination of the mole alone. The other two were placed in Groups IV and V, respectively. Their ultimate grading as chorionepithelioma in situ, irrespective of their original molar groups, was based on evidence of endometrial invasion. Such criteria were obtainable only from the removed uterus or adequate sections from the endometrium of the placental site. The designation for this small group of locally invasive, apparently malignant tumors, has been coined by us to include what we con-

sider a bona fide grade of chorioma. Whether it represents an early and, therefore, curable stage of true chorionepithelioma, we cannot say. Two examples of this highly malignant-appearing tumor are seen in Figs. 12 and 13. Both show evidence of exuberant trophoblastic overgrowth with pleomorphism and loss of basement membrane at the junction of the epithelium and stroma.

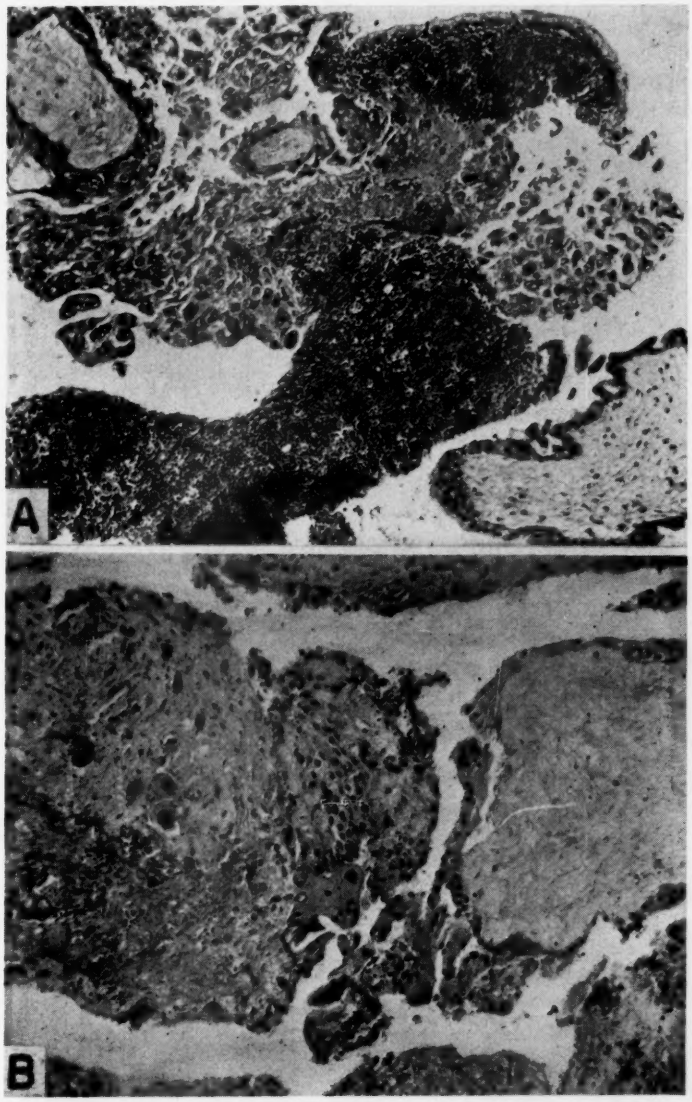

Fig. 11.—*A.*, A probably malignant hydatidiform mole (V) to show marked anaplasia and beginning tissue-culture-like growth of trophoblast. Patient developed chorioncarcinoma and died "within a year." Same case as Fig. 11, *B*. (M-100, ×110.)

B., Same case as Fig. 11, *A* to show placental site from uterus obtained at autopsy. Note relatively benign trophoblast attached to villus (right) and myometrium (left). This may be one of the rare examples of fatal chorionadenoma destruens, although the material available did not settle this point. (M-100, ×110.)

The latter is invaded by its own trophoblast in the specimen shown in Fig. 12, although the epithelium itself is not quite so malignant in appearance as that seen in Fig. 13. However, both specimens showed definite invasion of the endometrium, one example of which is illustrated in Fig. 13, *B*, and possessed the over-all morphologic criteria of chorionic malignancy. It is of interest to

note that the patient who passed the first mole is alive and well four years after its passage, while the second patient become normally pregnant one year later. Data on her delivery are not available.

B. Syncytial Endometritis

(Accentuation of syncytial placental site giant cells plus chronic infection)

This term represents the lowest grade of chorionepithelioma in all the standard classifications[2] of this type of tumor. We are in doubt as to whether it is a bona fide evidence of chorionic malignancy, although we include it as such in this study.

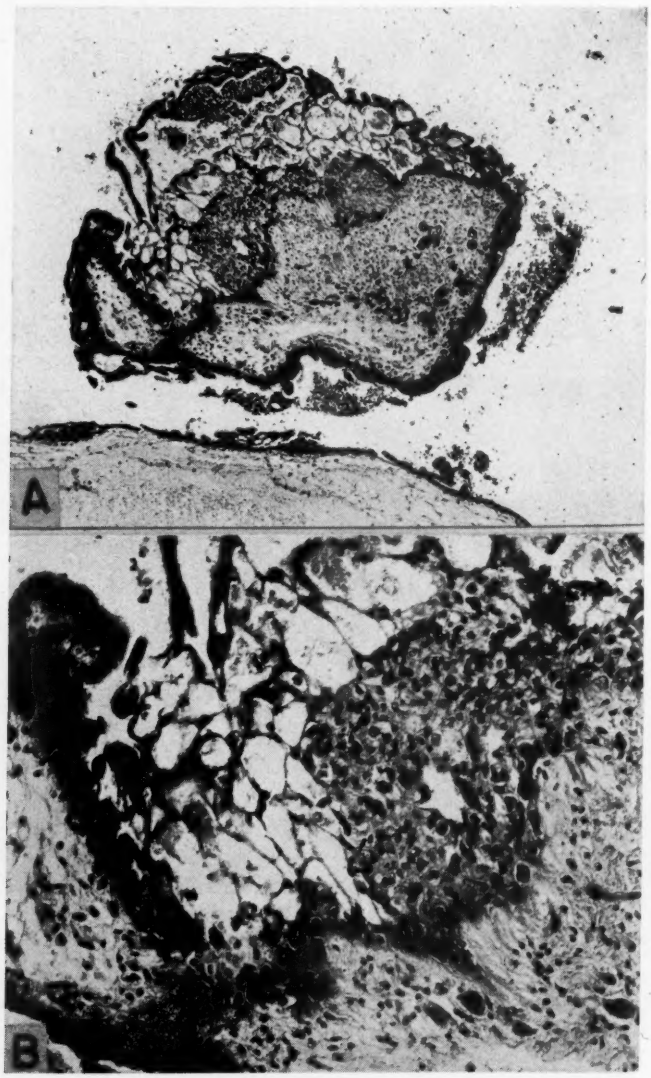

Fig. 12.—*A.*, A malignant hydatidiform mole (VI) to show marked growth and anaplasia of trophoblast with the latter invading its own stroma. Same case as shown in Fig. 12, *B*. Endometrium showed invasion by malignant appearing trophoblast constituting a chorionepithelioma in situ, but patient was well five years and seven months later. (M-10, ×50.)

B., Same case as Fig. 12, *A*, but in higher detail. Note loss of epithelial basement membrane and villous stroma invaded by its own trophoblast. (M-10, ×150.)

Of the nine cases in this general grade (Table II) only four were originally placed in the malignant Group (VI), the remainder having been placed in either Groups III, IV, or V. Their ultimate inclusion into this grade of malignancy is again based on evidence of myometrial invasion by the syncytial giant cells of the placental site (Fig. 14). That this type of invasion of the uterus by trophoblast does not always constitute true malignancy is shown by the case here illustrated. The patient in question passed a mole which we placed in Group VI. A subsequent curettage done on the sixteenth postpartum day yielded only a few fragments of myometrium and a little necrotic decidua. One of the myometrial fragments was from the placental site, and showed the

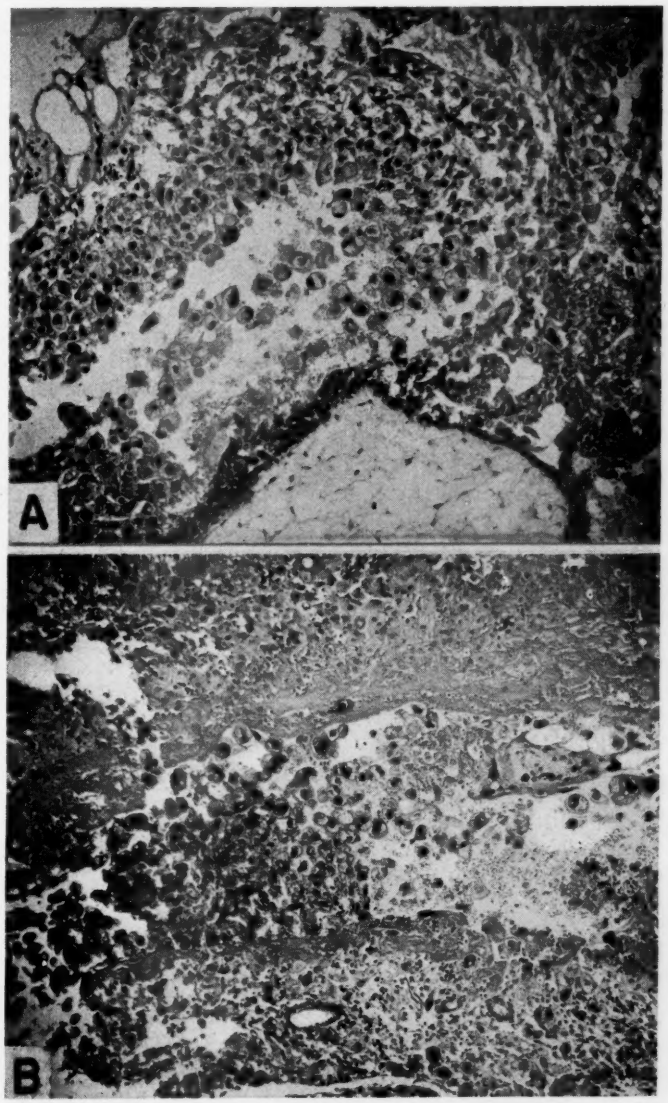

Fig. 13.—*A.*, A malignant hydatidiform mole (VI) with exuberant trophoblastic hyperplasia and anaplasia—the latter most marked in the cytotrophoblast. Same case as Fig. 13, *B.* (M-103, ×75.)

B., Same case as seen in Fig. 13, *A*, but showing endometrial invasion by anaplastic trophoblast similar to that of mole itself. This constitutes a chorionepithelioma in situ, and yet the patient was normally pregnant one and one-half years later. (M-103, ×130.)

picture seen in Fig. 14. A diagnosis of syncytial endometritis was returned and hysterectomy advised because of the malignant connotation implied by the term. The patient refused operation, but was living and well four years later. The case seemed so important to us that one of us personally visited the patient since she had refused to return to her original hospital. It would seem, at least in this instance, that the lesion in question does not constitute a true chorionic malignancy.

Whether such a lesion would ever go on to true clinical malignancy with continued invasion of the uterus and/or metastasis, we do not know. Of the 9 patients in this general grade, two are alive and well with their uteri seven

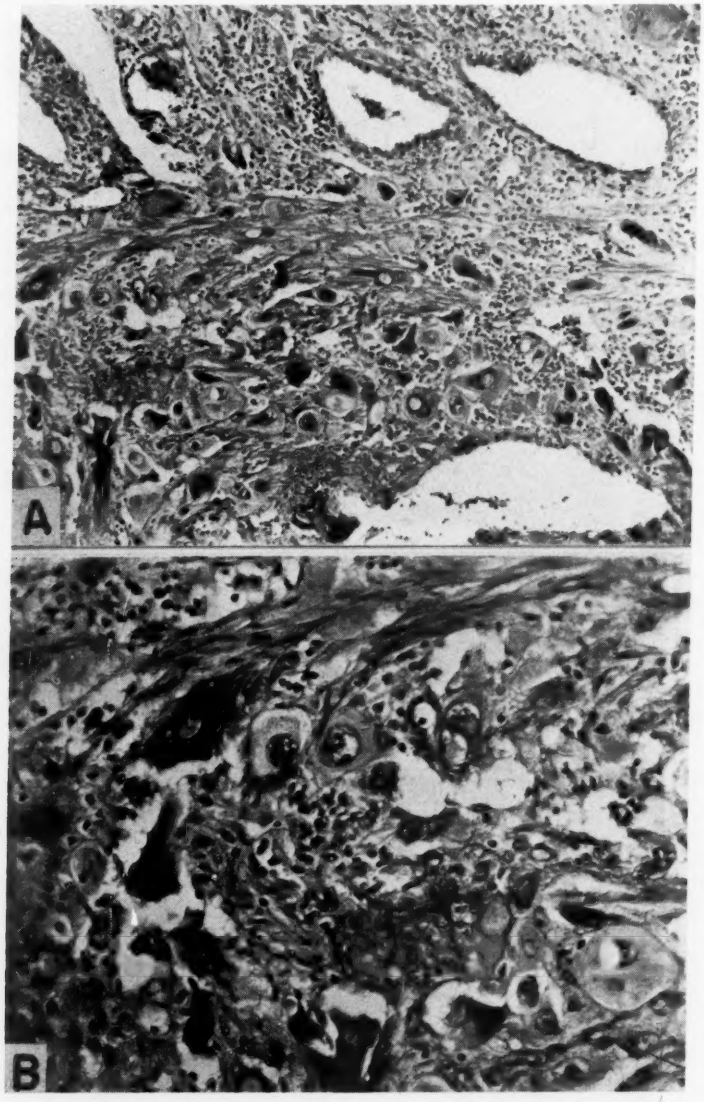

Fig. 14.—*A.*, The placental site illustrating syncytial endometritis curetted from a uterus which had previously contained a malignant mole (VI). Patient was alive and well four years and two months later with intact uterus. Higher power detail is seen in Fig. 14, *B*. (M-49, ×110.)

B., Same region of placental site from case shown in Fig. 14, *A*. These malignant-appearing syncytial giant cells are only slightly more anaplastic than those of a normal placental site. Note chronic inflammation. (M-49, ×250.)

months and four years, respectively, after delivery of the mole; the remaining seven all having had a hysterectomy. One patient died postoperatively of peritonitis, but the remaining 6 are alive and well three months to nine years later (Table IV). This is admittedly not a large series, although it would seem to us to indicate that the lesion is not often, if ever, truly malignant.

If this is a true but very low grade tumor and is merely an exaggeration of the picture seen in the normal placental site throughout pregnancy (except for the secondary chronic inflammation), it may offer a possible explanation of the rare chorioncarcinomas that are known to follow normal pregnancy, abortion, and ectopic pregnancy.

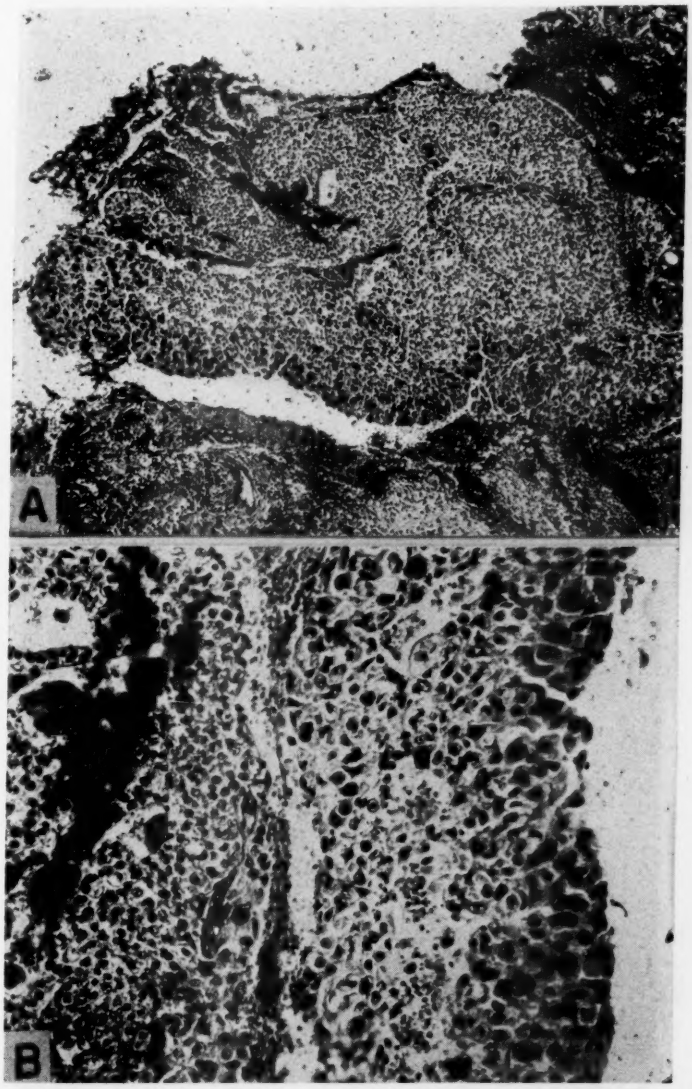

Fig. 15.—*A.*, Curettings obtained at time of evacuation of malignant hydatidiform mole (VI) showing markedly hyperplastic and neoplastic trophoblast. Latter shown at higher magnification in Fig. 15, *B*. Second curettage done five weeks later showed similar tissue. Uterus removed immediately and showed typical chorionadenoma destruens (see Fig. 15), but patient is still alive over ten years later. (M-16, ×50.)

B., Same trophoblast as seen in Fig. 15, *A*, but at higher magnification. Note extreme variation in degree of trophoblastic differentiation. (M-16, ×150.)

C. Chorionadenoma Destruens

(Invasion of myometrium by malignant mole but without metastasis)

This is the designation used to cover the group of chorionic malignancies which are characterized pathologically by persistent invasion of the myometrium by low grade malignant trophoblast, usually still attached to its parent villus. These tumors rarely, if ever, give rise to clinical evidence of metastasis and, therefore, the prognosis is excellent, provided the uterus is removed (Table IV). This group is characterized clinically by variable amounts of uterine subinvolution, postmolar vaginal bleeding, and usually a persistently

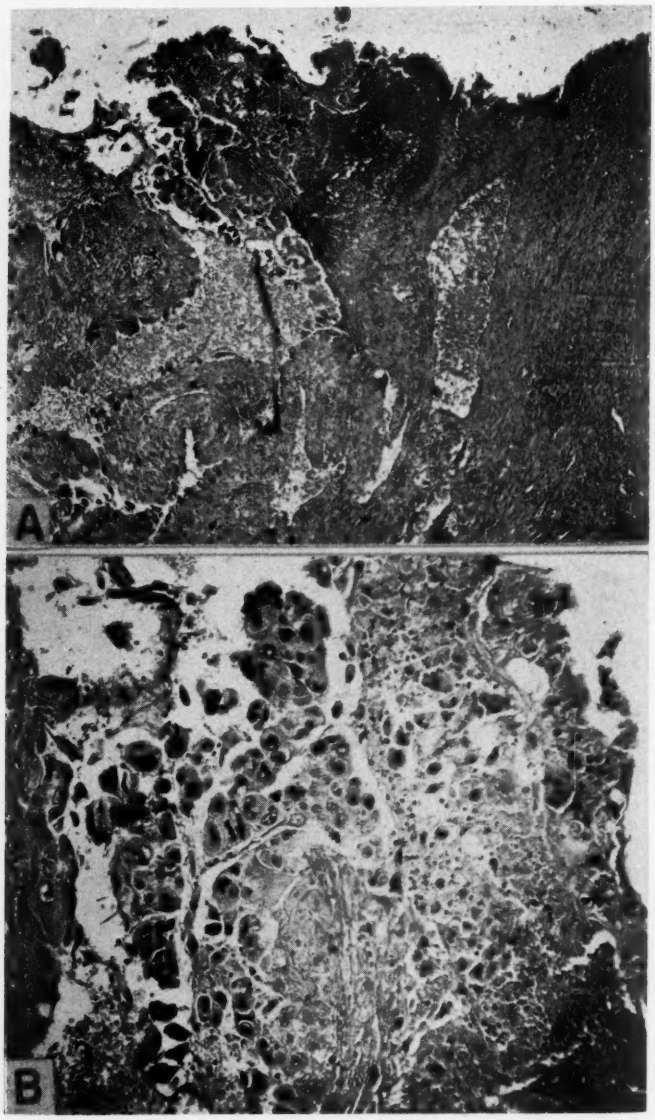

Fig. 16.—*A.*, Uterus from same case as seen in Fig. 15. Low power view of placental site to show invasion of myometrium by malignant-appearing trophoblast. The latter also lies partly with a vessel which opens into the uterine cavity. Higher power detail seen in Fig. 16, *B*. (M-16, ×50.)

B., Same placental site as shown in Fig. 16, *A*, but in more detail to show markedly anaplastic trophoblast. Patient is still alive over ten years later. (M-16, ×130.)

positive test for chorionic gonadotropic hormone. The rare perforating mole belongs in this category, of which we have one in this entire series of 200 cases. (The mole was morphologically malignant [Group VI] and perforated the uterus forty days after its passage, the patient being alive and well two and one-half years postoperatively.)

Of the 17 patients in the series originally diagnosed as having a malignant mole (Group VI), six were ultimately shown to possess chorionadenoma destruens (see Table II). Figs. 15 to 18 show the various pathologic features of this group. The moles are characterized by exuberant overgrowth of trophoblast (Fig. 15) with marked variation in its degree of differentiation. There

Fig. 17.—A typical example of a postmolar uterus showing a chorionadenoma destruens. The organ has been opened laterally, exposing the placental site at the fundus. The posterior wall has also been incised, one portion turned laterally to expose the blood-filled cavity made by the invasive hydatidiform mole. The deep seated lesion—inaccessible to the curette—may account for the low grading on this original mole, i.e., possibly malignant (Group IV). The microscopic appearance of this uterine lesion is seen in Fig. 18. (M-7, ×⅔ natural size.)

is often much benign hyperplasia with transitions to neoplasia. Such variations often occur in the same microscopic field (Fig. 15, *B*), a feature we have termed the "spread" phenomenon. When it occurs in any mole, we always place the specimen in the malignant group (VI) unless it is confined to only a few cells. The uterus from this same case shows invasion by similar tissue as seen in Fig. 16. The patient whose specimen is shown in Figs. 15 and 16 was alive and well ten years after hysterectomy. An example of a gross uterus

showing this process is seen in Fig. 17. Although the original mole was only a Group IV (possibly malignant) it is included here to show a typical gross uterus with this lesion. The latter is characterized by one or more hemorrhage nodules within the myometrium beneath the placental site. Hence the curette may not always reach the tumor. The cut surface of such an area often reveals a circumscribed cavity containing fluid and clotted blood. At the periphery of such a cavity is the invasive trophoblast responsible for the lesion (Fig. 18). Hydatid chorionic villi are often still attached to this epithelium or are lying free within the cavity. Because of the ultimate benign prognosis

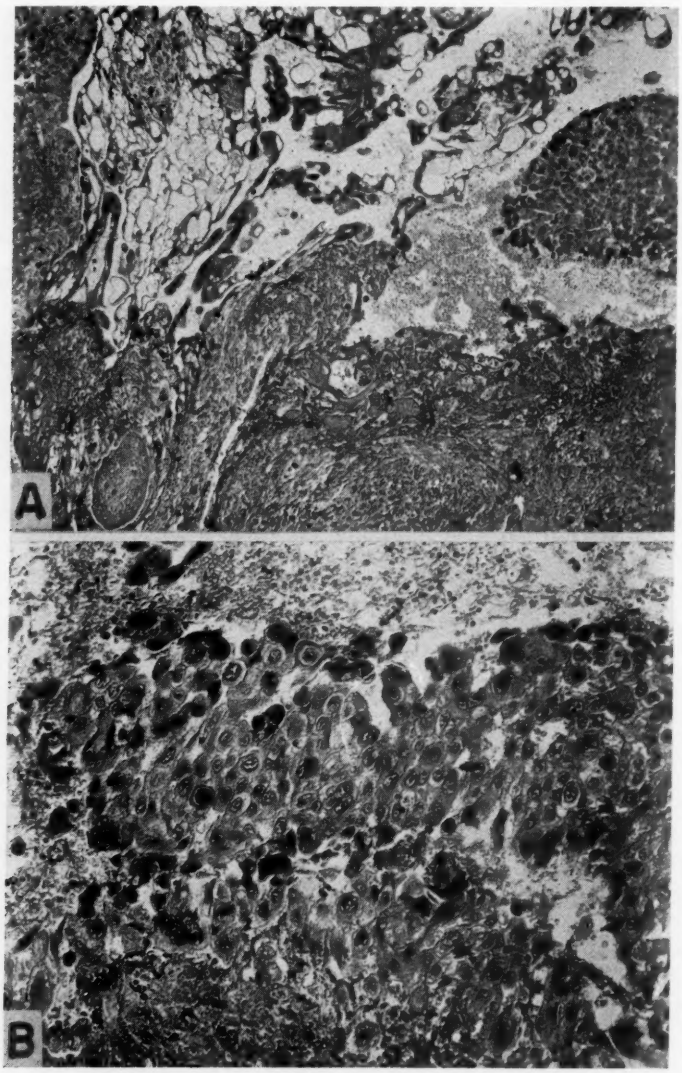

Fig. 18.—*A.*, A general view of the wall of a cavity within the myometrium of a uterus which is the seat of chorionadenoma destruens (see gross uterus in Fig. 17). Note both types of trophoblast, both only moderately anaplastic, but neverthelss invading the myometrium. The associated villus is not shown. Higher power detail of another portion of the lesion is seen in Fig. 18, *B*. This patient died five days postoperatively of peritonitis, so no follow-up data are available. (M-7, ×50.)

B., Markedly anaplastic trophoblast invading the myometrium from same case as shown in Figs. 17 and 18, *A*. (M-7, ×150.)

in such cases, providing a hysterectomy is performed, Ewing has designated this as chorionadenoma destruens. This highly descriptive term could be paraphrased as an "invasive mole." It rarely, if ever, metastasizes. In our entire series, 32 of the ultimate malignancies were of this type. None of the patients have died of chorionic malignancy (Table IV), although we have two or more years follow-up data on only 25 cases, roughly, 78 per cent. There was one postoperative death from peritonitis included in the 7 cases on which there

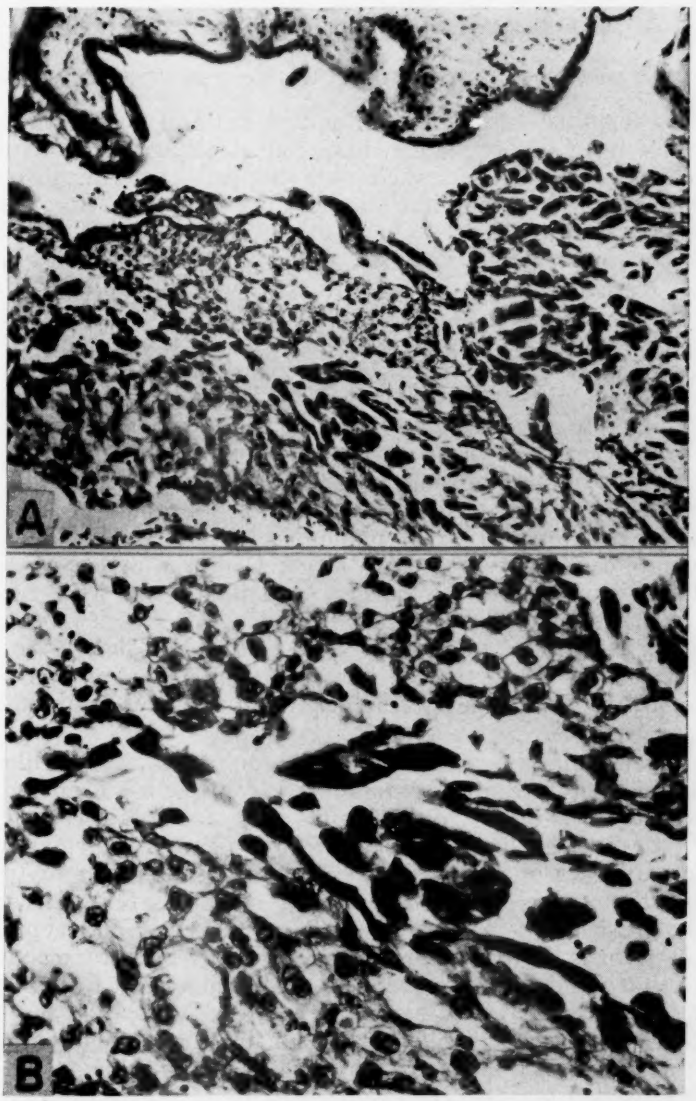

Fig. 19.—*A.*, A malignant hydatidiform mole (VI) showing marked hyperplasia of cytotrophoblast (middle left) and actual neoplasia of both trophoblastic elements (to the right and below). This is one of the two moles giving rise to chorioncarcinoma whose original mole or curetting showed a histologic pattern consistent with chorioncarcinoma. The patient was dead of brain metastasis within ten months. See Fig. 19, *B* for higher power detail of this trophoblast. (M-191, ×110.)

B., Same trophoblast as shown in Fig. 19, *A*. The hyperplastic trophoblast is seen in the upper portion of the photograph, whereas the neoplastic features of both elements are seen below. This picture is indistinguishable from the brain metastasis of the same patient as seen in Fig. 20, *A*. (M-191, ×250.)

are insufficient data to absolutely exclude the possibility of ultimate chorionic metastases. The two-year follow-up limit was arbitrarily set because all of our cases of chorioncarcinoma died within two years following the passage of the mole. This is in general agreement with the literature,[20] although various authors cite individual cases of death from this cause as late as eighteen years after the mole was delivered. These cases are a distinct rarity, even in a rare disease, and so may be disregarded for all practical purposes.

D. Chorioncarcinoma

(Variable picture in uterus but invariable metastases cause death)

This is the term used to describe the rare, fatal chorionic malignancy that may follow any form of pregnancy, but is most common (about 50 per cent) following moles. It is distinguished pathologically by metastases commonly to the lungs, brain, and vagina, but may involve other viscera. The metastases are pure chorionic epithelium without other villous elements, and possess a plexiform pattern of undifferentiated cytotrophoblast, the masses of which are more or less covered by immature syncytiotrophoblast. The uteri at autopsy often give no clue as to the highly malignant nature of the tumor. This fact has accounted for many references in the literature[2, 13, 15, 17] to fatal chorionepithelioma associated with disappearance of the primary tumor from the uterus. Indeed, three of our five fatal cases of this grade of chorionic tumor failed to show any true evidence of primary tumor at autopsy. A distressing feature in many of these cases is the lack of evidence on uterine curettage of the highly malignant nature of the tumor; as a result, the patient often dies with her uterus still intact. The moles from these patients, however, all show a high degree of morphologic malignancy, as shown by the fact that all 5 of our cases were placed in either Group V or Group VI, i.e., probably or definitely malignant. Whether even immediate hysterectomy would save these patients is a moot question, for Ewing[2] states that he has never seen a clinically cured case of true chorioncarcinoma. They, therefore, appear to be coincidentally malignant with respect to the pregnancy from which they arise. The various histologic characteristics of chorioncarcinoma are represented in Figs. 19 to 21.

The highly anaplastic nature of the original molar trophoblast is seen in Fig. 19. The mole was originally diagnosed by us as a VI, although what the original pathologist thought of it is not clear from our records. Unfortunately, the patient was lost track of after a negative curettage one month later. Follow-up data on her death were obtained from the medical examiner who performed a medico-legal autopsy nine months later. The metastasis to the brain is shown in Fig. 20, *A*. It is characterized by the typical plexiform masses of malignant cytotrophoblast covered by immature syncytiotrophoblast. (The morphology of metastasis varies from case to case, although in general they resemble the one shown. Those in the brain tend to be most photogenic, because their morphology is not obscured by blood.) The uterus in this case (Fig. 20, *B*) typifies the negative or equivocal character of the placental site in such cases. No tumor worthy of the name—certainly not a chorioncarcinoma—was found, although the vessels contained trophoblast undergoing fibrinoid degeneration. Whether this constitutes residual tumor we are not able to say. It certainly does not in any way resemble the metastases which caused the death.

In our series of 200 moles, five were followed by this form of tumor (Table II) although only two were originally placed in Group VI, the other three having been diagnosed as Group V. In one of the three latter cases we obtained material on both the mole and the curettings, the former showing a

Group V and the latter (Fig. 21) a Group VI morphology. Because we are attempting to correlate moles per se, we diagnosed this (mole), as only probably malignant, even though the curettings were highly malignant. In our experience, this and the previous one are the only two moles in the entire series of 200 whose original morphology or curettings are similar to the ultimate metastases which kill this type of patient.

All of our cases of chorioncarcinoma died as the result of their metastases within two years of the passage of the mole, the actual intervals being ten months, eleven months, "within a year," sixteen months, and two years,

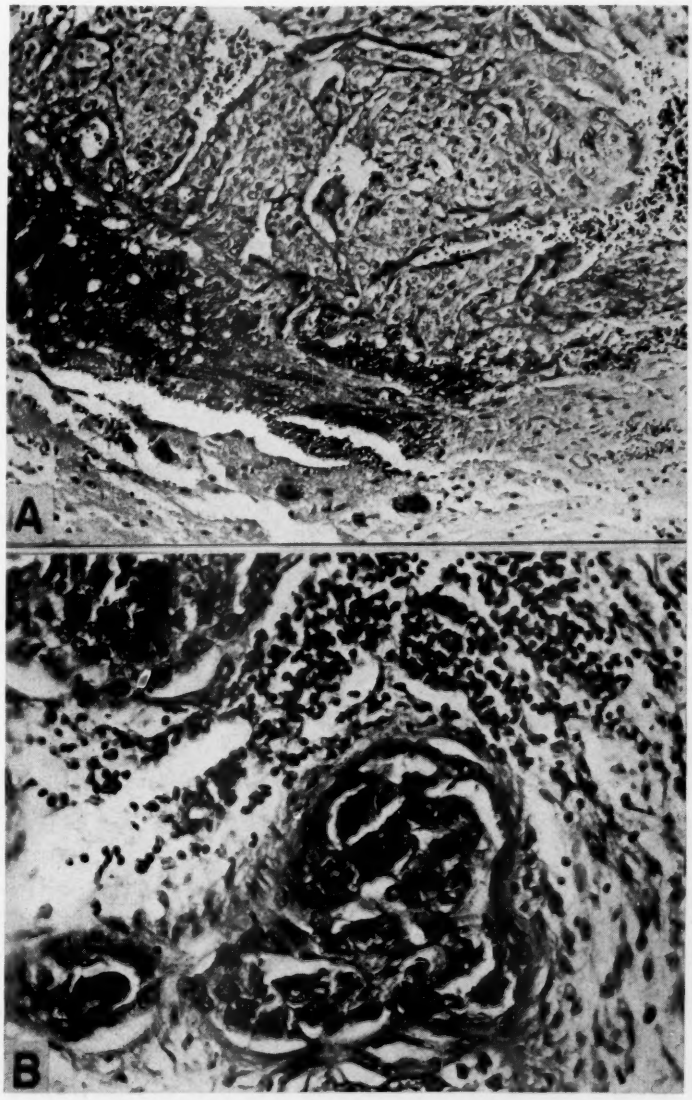

Fig. 20.—*A.*, Brain metastasis of chorioncarcinoma from same case shown in Fig. 19. Note identical morphology of metastasis and original molar trophoblast. Brain tissue is seen in the lower portion of the photograph. Same case as seen in Fig. 20, *B.* (M-191, ×110.)

B., Placental site from uterus obtained at autopsy of patient dying from chorioncarcinoma. Same case as illustrated in Figs. 19 and 20, *A.* This vessel contains trophoblast which is the seat of fibrinoid degeneration, but does not in any way resemble the trophoblast of the original mole or its metastases. (This case epitomizes the often negative or equivocal picture in the uterus of patients dying of chorioncarcinoma.) (M-191, ×250.)

respectively. Four of the five patients died with their uteri still intact, the fifth having had a hysterectomy about two years after the mole or a month prior to death. Of four patients who had a known uterine curettage within a month after the mole, two were definitely negative, one apparently not alarming, and only one showed evidence of tumor; and yet that patient did not come to hysterectomy, apparently because the original pathologist was not disturbed by what he saw in the curettings (Fig. 21). The other patient had no curettage after the mole, but the original pathologist was apparently not disturbed by what he saw in the mole (Fig. 11, *A*), for the patient did not come to hysterectomy. Curettage, therefore, seems to have been of little help

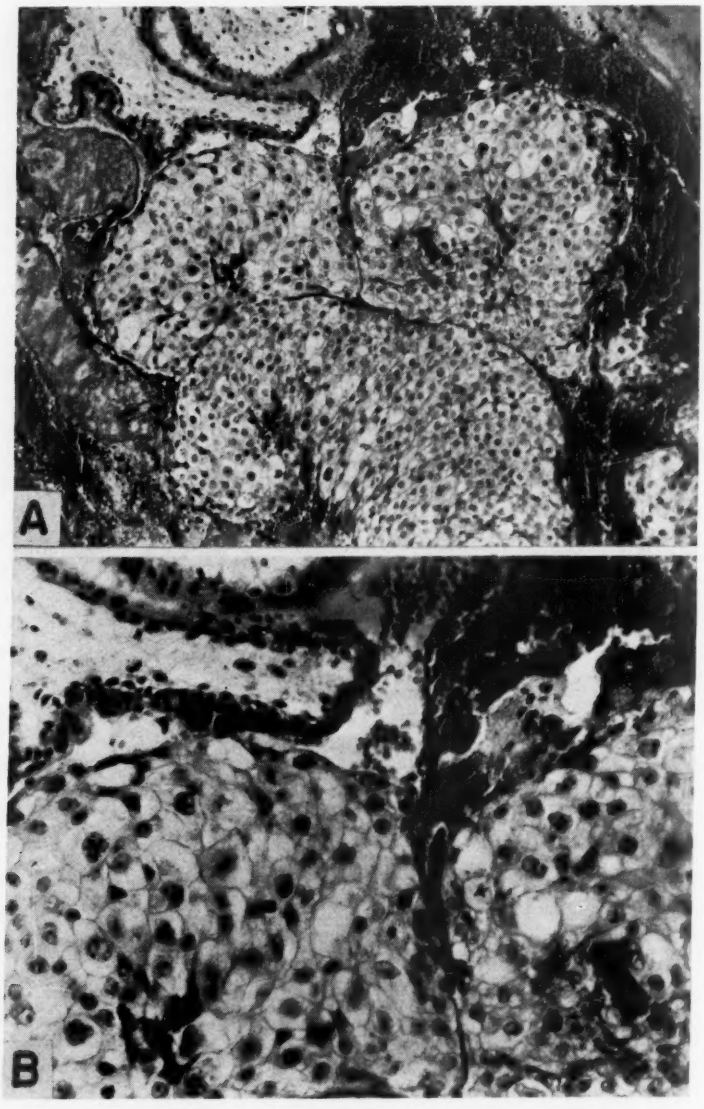

Fig. 21.—*A.*, Curettings of malignant mole (VI) obtained the day following the spontaneous delivery of a probably malignant hydatidiform mole (V). This is the second instance of original molar tissue resembling morphologic chorioncarcinoma. High power detail is seen in Fig. 21, *B*. Patient died one year later of chorioncarcinoma. (M-169, ×110.)

B., Higher power detail of malignant trophoblast from case shown in Fig. 21, *A*. Note benign-appearing villus at upper left. The large pale epithelial cells are malignant cytotrophoblast while the occasional dark cells are syncytiotrophoblast. (M-169, ×250.)

in making a correct diagnosis in our small series of chorioncarcinomas, although in one case (Fig. 21) it might have been. Furthermore, the equivocal or negative picture in the three uteri at autopsy, only two of which are illustrated (Figs. 11, *B* and 20, *B*), on which we have definite information, leads us to doubt whether even immediate hysterectomy would have cured any of these five patients. The possible exception is the case who showed residual tumor a month before her death. It will be recalled, however, that the curettage was not disturbing enough to indicate immediate hysterectomy. Unfortunately for our series, slides of that curettage were not available to us for study.

Discussion

From a general consideration of the data on these 200 hydatidiform moles there is shown to be a general correlation between the morphologic appearance of the original specimen and/or curettings and the subsequent development of some grade of chorionic malignancy. In other words, the more malignant the trophoblast of the original mole, the more chance the patient has of developing some grade of chorionepithelioma. These may vary from the locally invasive, morphologically malignant chorionepithelioma in situ with an excellent prognosis to the highly malignant, uniformly fatal chorioncarcinoma. This pathologico-clinical correlation is true, irrespective of whether all grades of ultimate malignancy or only the clinically malignant varieties of chorionadenoma destruens and chorioncarcinoma are considered.

In spite of the general correlation noted above, there is no absolute correlation in any individual mole between its original trophoblastic morphology and its histologic or clinical malignancy. Most of the clinically malignant grades, i.e., chorionadenoma destruens and chorioncarcinoma occur, however, in Groups IV, V, and VI, whereas all of the chorioncarcinomas are found in either Groups V or VI. With a large number of slides, carefully selected from many portions of the mole plus a meticulous study of curettings obtained *at the time of the molar evacuation,* there will be a more accurate pathologico-clinical correlation in these clinically malignant varieties. There is a suggestion, in our admittedly small series of chorioncarcinomas, that some areas of the original mole and/or the curettings resemble the ultimate metastasis. This was not invariably so, as has been mentioned before. Curettings done some weeks or months later may be of no help in evaluating either of these serious types of chorionic malignancies, since the primary tumor may have disappeared, metastasized, or buried itself in the uterus.

The lack of a specific pathologico-clinical correlation in any given case of hydatidiform mole is shown by the decreasing, yet definite percentage of patients having a benign clinical course, even in those moles diagnosed as probably (Group V) and definitely malignant (Group VI). That these clinically benign cases of hydatidiform mole, irrespective of their original molar group, are truly cured is shown by the high proportion of subsequent pregnancies: 49.6 per cent in the 147 patients for the first five groups. (Even two of the 53 patients showing some evidence of uterine invasion became subsequently pregnant, both in the chorionepithelioma in situ group. The latter patients, as a whole, had an excellent prognosis, as did those patients showing syncytial

endometritis.) Aside from the evidence of absolute cure, as shown by subsequent pregnancy, the probable cure rate in the clinically benign patients in the first five groups is significant: 36 out of 147 (24.6 per cent) alive and well two or more years following the mole. The possible cure rate in this group of patients is 18.3 per cent, or 27 out of 147 living and well less than two years. The remaining 11 patients (7.5 per cent) are the only ones in the clinically benign series of 147 on whom we have no follow-up. (They likewise constitute the only ones of the entire series of 200, or 5.5 per cent, on whom we have no evidence of what happened to the patient following her molar pregnancy. This is based on the reasoning that a subsequent hysterectomy—even though that patient subsequently had no follow-up—constitutes some degree of follow-up.) Thus, the combined prognostic or cure rate in these clinically benign series may be as high as 92.5 per cent.

The follow-up data on the histologically and/or clinically malignant moles may be summarized by the general statement that all cases except those of chorioncarcinoma have an excellent prognosis—even the chorionadenoma destruens. The latter is true only if such cases have a hysterectomy, because such tumors may kill by perforation, sepsis, or hemorrhage. Since these locally invasive but nonmetastasizing choriomas have a minimum probable cure rate of 78 per cent, or 25 out of 32 cases living and well two or more years after hysterectomy, it is apparent that they are not in danger of dying from subsequent metastases. That the probable cure rate is much higher—even 100 per cent—is indicated from the fact that none of the cases in this category have ended fatally, except the one patient who died of peritonitis five days postoperatively. Our lack of follow-up data on all 32 cases makes it impossible to say what happened to all of the cases. However, it would seem logical to assume that if any of these cases tend to have metastases, some of the 21 on whom we do have adequate follow-up data would have done so within two years after the molar pregnancy.

The probability that none of the chorionadenoma destruens are subject to metastasis appears to be of clinical significance. They form the largest single group who develop clinical malignancy, the 32 cases constituting 16 per cent of the entire series of 200 moles, as against the five cases of chorioncarcinoma which constitute only 2.5 per cent of the series. Since the former group can be benefited by proper therapy (hysterectomy), while the former probably cannot be benefited by any therapy, it behooves the clinician to be on the watch for evidence of a chorionadenoma destruens. All of our cases (except one who had only a persistent positive A-Z test) on whom we have adequate information, showed subinvolution of the uterus accompanied by bleeding. These occurred on an average within 35 days following the passage of the mole, although the extreme variations were five to one hundred twenty-six days in 19 cases. Four cases with immediate hysterectomy are excluded for obvious reasons in discussing the possibility of subinvolution and postpartum bleeding. The eight remaining cases in the series have insufficient data on which to draw any conclusions as to time or reason for hysterectomy.

In only one of the 32 cases (referred to above) was the uterus removed solely because of a persistently positive Friedman test (two and four weeks post partum). Since the test for chorionic gonadotropic hormone may remain positive for as long as sixteen weeks following the expulsion of a benign mole (Toland[19]), the average being three months, with variations of six days to ten months according to Payne,[16] it is obvious that it is of little help in diagnosing chorionadenoma destruens. However, postmolar vaginal bleeding and subinvolution of the uterus are almost invariably present, and indicate the need for at least a uterine curettage, with the probability of a subsequent hysterectomy. Curettage in this series of chorionadenoma destruens was often done, showing that the operation per se does not increase the danger of subsequent metastasis.

Summary

In view of the proved curability, all grades of chorionic malignancy except chorioncarcinoma, regardless of how the latter is treated, it seems reasonable to adopt a conservative attitude regarding the pathologico-clinical approach to the problem of hydatidiform moles. An adequate pathologic examination of molar tissue *and curettings, done at the time of operation,* is valuable but not of absolute diagnostic or prognostic significance. The more malignant the mole appears morphologically, the more likely the patient is to develop some form of chorioma. Therefore, the clinician should be apprehensive regarding clinical malignancy in proportion to the degree of apparent pathologic malignancy. Such clinical malignancy (except in some chorioncarcinomas) is usually indicated by subinvolution of the uterus and bleeding, which indicates the need for a repeat curettage and probable hysterectomy. Chorionic gonadotropic hormone tests are of little or equivocal value during the period when treatable clinical malignancies are first developing, i.e., on an average thirty-five days after the expulsion of the mole. By thus adopting a conservative attitude of "scientific apprehensive expectancy" (courtesy of Dr. F. C. Irving) many uteri will be saved that are now needlessly removed without adding appreciably—if any—to the death rate from chorionic malignancy.

Conclusions

1. A series of 200 hydatidiform moles, gathered consecutively over a period of eleven years from 109 medical communities in the eastern half of the United States, have been examined.

2. Follow-up data on 94.5 per cent of all patients are available.

3. Microscopic criteria of six groups of hydatidiform moles have been described and illustrated. These show a marked, but not an absolute correlation between the degree of apparent molar malignancy and the tendency of the patient to develop some grade of chorionic malignancy.

4. In 73.5 per cent of the entire series there was no subsequent development of either pathologic or clinical malignancy, as judged from the follow-up data available on 90.5 per cent of this particular group.

5. In 26.5 per cent of the entire series, the various grades of chorionic malignancies occurred as follows:

a. Chorionepithelioma in situ	3.5 per cent
b. Syncytial endometritis	4.5 per cent
c. Chorionadenoma destruens	16.0 per cent
d. Chorionecarcinoma	2.5 per cent

6. The prognosis of all grades of chorionic malignancy is excellent, except for the relatively uncommon, invariably fatal chorioncarcinoma, as judged from the follow-up data available on 89 per cent of this entire malignant group.

7. In the first three grades of chorionic malignancy, all curable if properly treated, clinical evidence of malignancy is usually shown by continued postmolar vaginal bleeding and/or subinvolution of the uterus.

8. A policy of clinical watchful waiting may be followed until such objective evidence of malignancy develops without increasing the danger to the patient from chorionic metastasis.

9. Such individualized clinical conservatism will thus save many uteri that might otherwise be needlessly sacrificed in haste merely because the patient has passed a hydatidiform mole.

References

1. Chandra Das: J. Obst. & Gynaec. Brit. Emp. **45**: 265-280, 1938.
2. Ewing, J.: Neoplastic Diseases, a Treatise on Tumors, Philadelphia, 1940, W. B. Saunders Co., pp. 608-623.
3. Fraenkel, Eugen: Neue Folge Gynäk. **180**: 69-91, 1897.
4. Hertig, A. T., and Edmonds, H. W.: Arch. Path. **30**: 260-291, 1940.
5. Hertig, A. T., and Rock, J.: Carnegie Inst. Wash., Pub. 525, Contrib. to Embryol. **29**: 127-156, 1941.
6. Hertig, A. T., and Rock, J.: Am. J. Obst. & Gynec. **47**: 149-184, 1944.
7. Hertig, A. T., and Rock, J.: Carnegie Inst. Wash., Pub. 557, Contrib. to Embryol. **31**: 65-84, 1945.
8. Hertig, A. T.: Yale J. Biol. & Med. **18**: 107-115, 1945.
9. Heuser, C. H., Rock, J., and Hertig, A. T.: Carnegie Inst. Wash., Pub. 557, Contrib. to Embryol. **31**: 85-99, 1945.
10. Mallory, T. B.: New England J. Med. **220**: 251-252, 1939.
11. Mathieu, A.: Int. Abst. Surg. **68**: 52-70, 1939.
12. Mathieu, A.: Int. Abst. Surg. **68**: 181-198, 1939.
13. Maun, M. E., and Green, W. M.: Am. J. Obst. & Gynec. **46**: 738-743, 1943.
14. McLaughlin, E. F.: Am. J. Obst. & Gynec. **42**: 904-907, 1941.
15. Novak, Emil, and Koff, A. K.: Am. J. Obst. & Gynec. **20**: 153-164, 1930.
16. Payne, F. L.: Surg., Gynec. & Obst. **73**: 86-95, 1941.
17. Rubin, I. C.: Am. J. Obst. & Gynec. **41**: 1063-1068, 1941.
18. Tenny, B., and Parker, F., Jr.: New England J. Med. **221**: 598-599, 1939.
19. Toland, O. J.: Am. J. Obst. & Gynec. **44**: 502-504, 1942.
20. Vineberg, H. N.: J. Mt. Sinai Hosp. **10**: 12-32, 1943.
21. Williams, T. J.: Am. J. Obst. & Gynec. **45**: 433-444, 1943.
22. Wilson, K. M.: Am. J. Obst. & Gynec. **38**: 824-838, 1939.
23. Wislocki, G. B., and Bennett, H. S.: Am. J. Anat. **73**: 335-449, 1943.

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Discussion

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—I am impressed with the industry with which this material has been collected, the care and diligence of its study, and the logical effort the essayist has made to evaluate his findings.

The difficulties and problems in this field are many; Dr. Hertig has mentioned a few of them:

(1) The difficulty of securing representative and significant materials for study—the surgeon submitting the gross material evacuated, but often failing to submit separately the curettings of tissue which was in direct contiguity with the uterine wall. The latter, of course, is extremely important in an evaluation of the malignant propensities of the growth.

(2) The variable nature of growth activity in molar tissue, and the difficulty of "pigeonholing" lesions. In this direction the Ewing classification of malignant types seems cumbersome and not too meaningful, for each mole differs from another in structural appearance and biologic behavior.

(3) The tendency of these tumors to follow in their behavior their trophoblastic prototypes makes prognostication uncertain.

(4) In view of these several considerations, the establishment of standards of malignancy is in this field especially difficult—anaplasia, pleomorphism, invasion, portability, persistence at placental site, and ultimate lysis in all situations being features not only of "malignant" mole, but also of physiologically and embryonically normal syncytium.

The very skeptical may say that the only sure proof of malignancy in mole is the autopsy finding in the dead patient, and point to the fact that of the 117 patients in Hertig's Group IV, V, and VI, only 47 were proved to have malignancy, even upon the conditions which he has set forth. This statement in no way detracts from the importance of the paper, but points simply again to the intricate nature of this problem, and indicates that the pathologist is still going to be unable, oftentimes, to give us an absolute yes or no to the malignancy of molar tissue.

What Dr. Hertig has set out to do, and what he has accomplished as far as seems humanly possible, is to set up groups of cases within which the similarity of histologic findings indicates that malignant manifestations may be anticipated in a rather uniform percentage of cases. Then he who rides may read.

This matter is important both to the pathologist and the clinician. To the pathologist seeing only occasional material, it provides a standard for histologic comparison. To the clinician it provides something more than silver-ball conjecture as to what the prospects of his case may be. I surmise that Dr. Hertig had no further purpose than this in mind and, like all real students of his subject, he is content to add to our knowledge these few important observations.

In conclusion, I would say that this contribution has "squeezed the orange dry" as far as histologic study of hydatidiform mole is concerned, and that further progress in this field will have to wait upon the studies of the biologist and enzyme chemist who may ultimately tell us why in some instances the mole destroys the host and in others the host dissolves and eliminates some of even the most malignant-appearing moles.

DR. ROBERT A. ROSS, Durham, N. C.—The essayist, by painstaking study of specimens and careful follow-up of patients, has been able to predict malignancy in very high percentage of instances and, with known methods of treatment, should favorably influence the mortality from the malignant chorionic tumors. The fact that it appears impossible, from examination of the mole itself, to state the definite malignancy that the mole will ultimately exhibit is not so noteworthy as is the correlation between the microscopic appearance of a mole and evidence of malignancy in the uterus. We know that this bizarre tumor manifests itself in varying degrees of malignancy, extension, progress, and prognosis, yet by prompt, judicious surgery and deep x-ray therapy we can promise relief, with the exception of those who have chorioncarcinoma, to the majority of these patients.

This report also substantiates the observations of most men regarding such studies; the highly malignant carcinoma is relatively rare. Thus the essayist has satisfactorily dealt with the hydatidiform mole and the malignancy that often follows. However, we know that at least one-half of these malignant tumors follow other types of pregnancy or pregnancy complications. Diseases of the chorion are common, but hydatidiform mole is rare. When the uterus and associated mechanism of defense cannot destroy chorionic tissue, one should immediately be alert to the possibility of chorionic malignancy. This inability to prevent chorionic sustenance and growth is evidenced by abnormal bleeding

and the histologic appearance of tissue as described. In the study of the autopsy material in our patients, who did not have a history of previous hydatidiform mole, we noted a difference in the degree of malignancy and appearance between the cells in the uterus and the cells in the lungs. In one patient with tubal pregnancy, the malignancy was found only on careful recheck of the material after x-rays of the lungs were suggestive of metastases.

If our understanding of the histology and hormonology of these tumors is correct, it is difficult to explain a negative chorionic gonadotropin assay, except it be due to faulty animals, specimens, or technique.

It is generally agreed that assays for chorionic gonadotropin are of very definite value in diagnosing and following cases of hydatidiform mole and chorionepithelioma.

A negative qualitative test in the face of frank evidence of a mole or following removal of malignant chorionic tissue, conveys to the investigator not only a sense of relief, but also one of doubt. An initial negative test should be checked immediately and, if still negative, tests should be repeated at frequent intervals. The frequency and duration of this repetition should be governed by clinical evidence.

Positive qualitative tests also may be viewed with suspicion under certain circumstances. If the more common causes of excessive gonadotropin production in women can be ruled out, one probably is justified in assuming a state of emergency exists in instances where the presence of a mole is suspected or in which there is reason to believe a mole has been passed. If a positive test can be correlated with factual evidence of a mole, there should be no hesitancy about institution of immediate measures.

Positive qualitative tests obtained with spinal fluid still are considered of positive diagnostic import. We find, however, that a negative test obtained with spinal fluid is not always of diagnostic value.

Quantitative assays for chorionic gonadotropin need be done only following detection of this substance by qualitative tests.

We have come to realize that it may be unfortunate to place great emphasis, as regards diagnosis, on the so-called "large amounts" of chorionic gonadotropin excreted in instances of malignant moles and chorionepithelioma. It has been shown on a number of occasions that the values of gonadotropin excretion in some cases are very much lower, and often no greater, than those found during a corresponding period of normal pregnancy.

When clinical manifestations indicate investigation of a pregnancy that has progressed beyond ninety days, and if maintained or increasing gonadotropin levels are found, then the presence of a mole or chorionic malignancy should be ruled out. If the pregnancy had advanced into the last trimester, a diagnosis might have to be made between toxemia of pregnancy and chorionic cancer.

During the past 15 years at Duke University we have treated seven patients with diagnosed hydatidiform mole and five patients with diagnosed chorionepithelioma, and have studied tissue from 12 additional patients. None of the malignancies followed moles, and none of the seven patients with mole, on whom we have adequate follow-up data, has developed chorionepithelioma, though one classed as doubtful, who refused operation, had intermittent bleeding and positive chorion gonadotropin tests for a year. Three had subsequent pregnancies. One malignancy followed a tubal pregnancy. The elapsed time from the last pregnancy until diagnosis of chorionepithelioma varied from two months to four years, with death in two months to three years.

It is hoped that the essayist's presentations will lead to a clearer understanding of the malignancy potentialities of the mole and a better classification of the chorion malignancies. Perhaps the use of three groups for the hydatidiform mole and designating the malignancies by grades, such as the adenomas and carcinomas of other groups, would lead to clarifications and unanimity. The advantage of a repository for such malignant tumors is suggested.

DR. EMIL NOVAK, Baltimore, Md.—It is because I am afraid that Dr. Hertig's paper may exert a harmful influence that I feel impelled to express disagreement with some of his observations. In the first place, he places 53 of his 200 cases of mole in the

malignant group, a startling proportion. This statement in itself might well lead some to more radical treatment of hydatidiform mole than is actually justified. Many years ago I reported a series of, I believe, 11 moles, all treated by simple evacuation of the uterus, and none developing any manifestations of malignancy. At the same meeting, the late J. Whitridge Williams and J. B. DeLee reported even larger groups, with the same conservative therapy and the same absence of unpleasant sequelae. The seven cases in Dr. Hertig's series which terminated fatally were obviously chorionepitheliomas, and the slides of the two or three cases of this group which he threw on the screen showed this very clearly.

But in his 53 malignant cases, Dr. Hertig has included many which he apparently puts into this group on the basis of a histologic evaluation which, I think, is fallacious. I have seen any number of moles with just as much trophoblastic proliferation and just as much evidence of what he calls anaplasia, in which the clinical course was entirely benign. Anaplastic activity is far more difficult to establish in trophoblast than in ordinary epithelial or connective tissue elements. Huge hyperchromatic nuclei are common even in normal trophoblast, and so is destructiveness and invasiveness, and so is the physiologic form of metastasis which we call deportation of villi or trophoblast.

After all, chorionepithelioma is an exceedingly rare disease, and in some very large clinics not a single case has been observed. Benign hydatidiform mole is far more common, and I personally do not believe that much more than 1 per cent of moles become actually malignant, though a wrong diagnosis to this effect has a much higher incidence. To lay down such histologic criteria of malignancy as does Dr. Hertig is not justified unless it can be supported by clinical evidence, which in the malignant choriomas usually means the death of the patient.

There is usually no great difficulty in the microscopic diagnosis of the frankly benign or the frankly malignant cases, but there is a small group in which pathologists will differ, and to which such terms are applied as malignant mole or chorionadenoma destruens, although I think the latter designation, suggested by Ewing, a very poorly selected one. This group, characterized clinically by a lower degree of malignancy, and especially by extensive intravascular penetration, seems to me to bear the same relation to chorionepithelioma as does an adenocarcinoma of Grade I to one of Grade III or IV. In other words, one encounters all gradations of benign or malignant neoplastic activity in the chorionic epithelium as on any skin or mucous membrane surface. The simplest concept is that of two groups, the benign and the malignant chorioma, although in this field, as in all others in pathology, there is a small borderline group, of suspicious or slight malignancy, in which there is bound to be difficultiy in microscopic interpretation.

Finally, and it seems to me rather paradoxically, in view of what he has presented to us in his paper, Dr. Hertig advises a conservative plan of management of hydatidiform mole, with which most of us will fully agree.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—Management of this interesting problem resolves itself into two objectives: the diagnosis and removal of malignant chorionic tissue while it remains localized in the pelvis, and the avoidance of unnecessary surgery during the childbearing age because of the fear that malignant chorionic tissue might be present.

In the past, only two approaches to this problem were available: first, the clinical picture of each case, and second, the microscopic traits of tissue that was removed or expelled. Recently, a third approach, hormone studies, have proved to be of such great value that they are considered by some to be the most important of the diagnostic procedures.

Dr. Hertig's work will prove to be a valuable contribution to the subject of mole and chorionepithelioma, and his stand is to be admired, particularly in view of the great hesitation that has been voiced by numerous eminent pathologists, including Pick, Frank, and Novak, who have pointed out the marked difficulty that attends the attempt to evaluate the malignant properties of chorionic tissue by means of microscopic examination. Because of this difficulty, the diagnostic possibilities of hormone analysis were eagerly seized upon by students of the subject.

Since the production of chorionic hormone is one of the properties of chorionic tissue, whether normal or abnormal, the body fluids of a person harboring such tissue would be expected to contain demonstrable quantities of this secretion. This expectation has been confirmed and has been attested by many investigators during the last ten or fifteen years. Quantitative assays of the chorionic hormone have proved to be invaluable as an aid in the early diagnosis of hydatidiform mole. Following removal or expulsion of the mole, except in rare instances, regularly spaced hormone titration of the blood serum has been shown to permit differentiation between recovery and the development of chorionepithelioma. On one hand, a gradual decrease, or the lack of an increase, in the chorionic hormone—even over an extended period of observation—indicates the absence of chorionepithelioma. On the other hand, an increase in the prolan values denotes the presence of a malignant process or of an intervening pregnancy. The latter condition may be proved or disproved by such assays, for the characteristic hormone peak of early pregnancy does not occur in the presence of chorionepithelioma. The hormonologic identification of chorionic malignancy rests not upon a single quantitative or qualitative determination, but upon the demonstration of increased values by means of repeated assays. Deliberate consideration of the clinical, the microscopic, and the hormone picture of each such problem will permit the effective separation of those who require radical treatment from those for whom such treatment would consist of needless mutilation.

DR. HERTIG (Closing).—In answer to Dr. Novak's question regarding the high proportion of malignancies in this series, namely, 53 out of 200 cases, it must be emphasized that such malignancies included various grades of histologic and/or clinical malignancy. Thus, there were seven cases we called chorionepithelioma in situ, two of the women subsequently had babies, while the remaining five were living and well either with or without their uteri one and one-half to five and one-half years later. The nine cases whose uteri showed syncytial endometritis, a pathologic entity recognized by the late James Ewing, all ran a clinically benign course, except the one patient dying postoperatively of sepsis. The 32 cases of chorionadenoma destruens, or locally invasive mole, likewise ran a clinically benign course, although it is recognized that such a condition may ultimately kill the patient by uterine perforation, sepsis, or hemorrhage, even though there is no clinical evidence of metastasis. There remain only five cases of chorioncarcinoma, about which there can be no argument as to their ultimate malignancy, since all died of metastases within two years. Since it is apparent that there are various histologic and/or clinical grades of chorionic malignancy, it becomes imperative to distinguish between them, rather than to designate them all as chorionepithelioma.

Dr. Payne's question regarding the value of hormone tests with respect to the diagnosis of chorionic malignancy following a mole is well taken. Perhaps I did not make this matter clear, but what I endeavored to point out, based on Dr. Payne's own data, was that during the first month after evacuation of a mole, the qualitative chorionic gonadotropic hormone tests were of equivocal value because they remain positive, on an average, three months following a benign mole, with variations of six days to ten months. Since this interval coincides roughly with the average postmolar period of thirty-five days during which treatable forms of chorionic malignancy show uterine bleeding and/or subinvolution, it is better to rely on such clinical criteria rather than qualitative hormone tests alone in determining whether a uterus should be removed. Quantitative hormone tests, however, are of great value in evaluating the period following molar evacuation, since they usually show not only the presence of viable trophoblast, but whether it is increasing or decreasing in amount.

In conclusion, I wish to emphasize that the treatment of a patient harboring a hydatidiform mole should be individualized, and that this often difficult problem needs all the hormonal, clinical, and pathologic data obtainable for its solution.

CONGENITAL MALFORMATIONS ASSOCIATED WITH DEVELOPMENTAL DEFECTS OF THE FEMALE REPRODUCTIVE ORGANS*

LAWRENCE R. WHARTON, M.D., BALTIMORE, MD.

THE study of congenital defects of the genitourinary system has been facilitated in recent years by developments in intravenous urography, endocrinology, and embryology. Interest in these malformations has been increased by the evolution of new operative measures, by which some of them may be corrected or ameliorated. With this in view, it seemed worth while to survey the subject of congenital malformations of the female reproductive organs, especially with respect to the associated developmental defects.

I shall consider first, congenital malformations of the ovary, especially agenesis of the follicular epithelium, a condition recently described by both European and American observers. In America, this condition has been studied particularly by Albright and his associates,[12] and Wilkins and Fleischmann.[7, 12] We shall then consider the various malformations due to faulty development of the Müllerian ducts and the cloaca.

Agenesis of the Ovarian Follicular Epithelium

Pathology: The term "ovarian failure" has been used for years in gynecologic and endocrinologic parlance. In the past, it has generally been assumed that ovarian failure was secondary to some endocrine disorder, marked by a lack of normal gonadotropic stimulation of the ovaries and subsequent absence of function, or disordered function, of the ovaries. Although this is undoubtedly the explanation of many cases of ovarian dysfunction, Albright and Wilkins and Fleischmann[7, 12] have isolated from this heterogeneous group one syndrome in which this explanation does not hold. In this group, they have found that the ovarian failure is due to agenesis and lack of follicular epithelium; the ovary is hence quite incapable of function, regardless of the efficiency of the gonadotropic hormones.

The characteristic feature of this condition is the rudimentary development of the ovaries and the complete absence of any ovarian follicular epithelium (Fig. 1).

The microscopic appearance of the ovary in agenesis of follicular epithelium is shown in Fig. 2. Serial sections of one ovary of this young woman failed to show any trace of ovarian follicles.

In these cases, the absence of any follicular activity produces characteristic sequelae. The uterus, Fallopian tubes, vagina, external genitals, and breasts remain undeveloped. The condition of the uterus and Fallopian tubes is shown in Fig. 1. Pubic and axillary hair may be present, due to the activity of the androgens (Albright).

Clinical features: The essential gynecologic characteristics are the lack of development of the reproductive organs and breasts, amenorrhea, and lack of function of the ovaries. In contrast with this, the function of all of the other endocrine glands is normal. The level of the follicle stimulating hormone (F. S. H.) is high, as it is after castration or the menopause; the 17-ketosteroids are low.

*Read (by invitation) at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

These findings, together with the pathologic histology of the ovaries, clearly distinguish these cases from ovarian dysfunction due to disorders of other endocrine glands in conditions such as Froehlich's or Cushing's syndromes, or cretinism.

In 1944, Wilkins and Fleischmann reported three such cases, proved by histologic examination of the ovaries. These cases were identical with the syndrome previously reported by Albright and his associates without pathologic proof. They also were identical with cases that had been reported by German observers, some of which had been proved histologically. In 1946, Wilkins and Fleischmann reported that they had seen 13 such cases. This makes a total of about 50 cases of agenesis of the ovarian follicular epithelium that have so far been reported in the literature. From this, one would judge that the condition is not extremely rare.

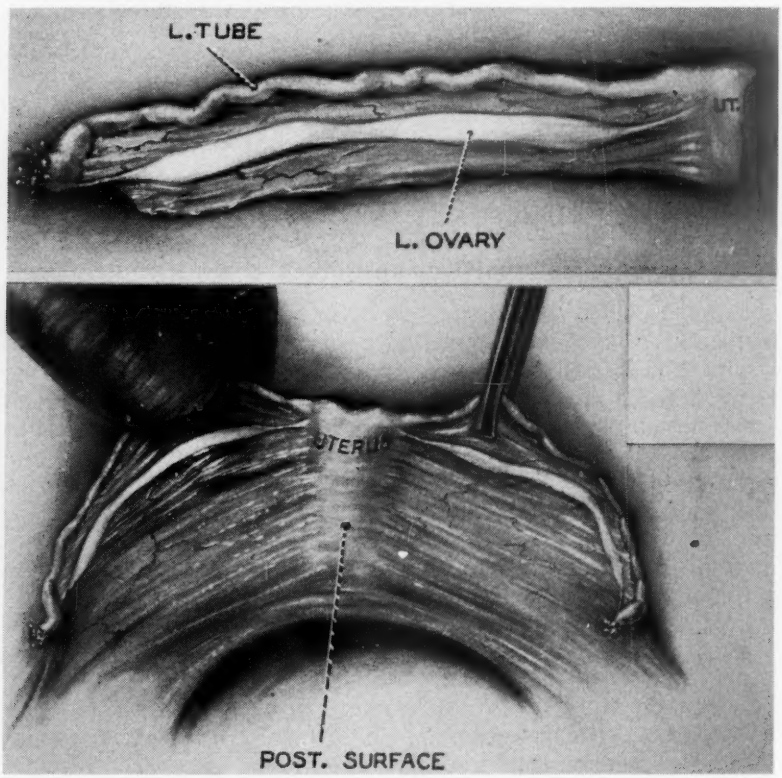

Fig. 1.—Agenesis of follicular epithelium of ovary in a young woman almost 18 years of age. The reproductive organs are rudimentary. The Fallopian tubes are hardly more than threads. The uterus measures 3 cm. long and 1 cm. in diameter. Each ovary is an elongated ridge of white tissue, 3 mm. in diameter, about 2½ cm. long. (From Wilkins and Fleischmann. J. Clin. Endocrinol. 4: 357, 1944.)

As a matter of clinical observation, I wonder whether there are not also instances of partial agenesis, as well as complete lack of ovarian follicular epithelium—in other words, in which the number of ovarian follicles is decreased, but not altogether lacking. Possibly this may be the explanation for some cases of marked oligomenorrhea, in which the patient menstruates only once or twice a year. Some of these women have no other endocrine disorder, and bear children. In some instances, furthermore, the oligomenorrhea is clearly a familial characteristic, shared both by mother and daughters. This would again suggest the

genetic, or hereditary, nature of the disturbance. If this explanation is tenable, it explains the futility of gonadotropic therapy in such situations.

Malformations associated with agenesis of the follicular epithelium: The genetic nature of the condition is further attested by the associated congenital anomalies. In the 32 cases first collected and reported by Wilkins and Fleischmann, they listed the following associated malformations: retardation of the growth resulting in short stature, coarctation of the aorta, webbed neck, defects of the eye, congenital deafness, spina bifida, and mental retardation. These were probably entirely independent genetic faults, indicating the widespread defectiveness of the germ plasm. There were also occasional acquired defects, such as osteoporosis, which was probably due to the ovarian insufficiency, and also hypertension, the cause of which was not always clear.

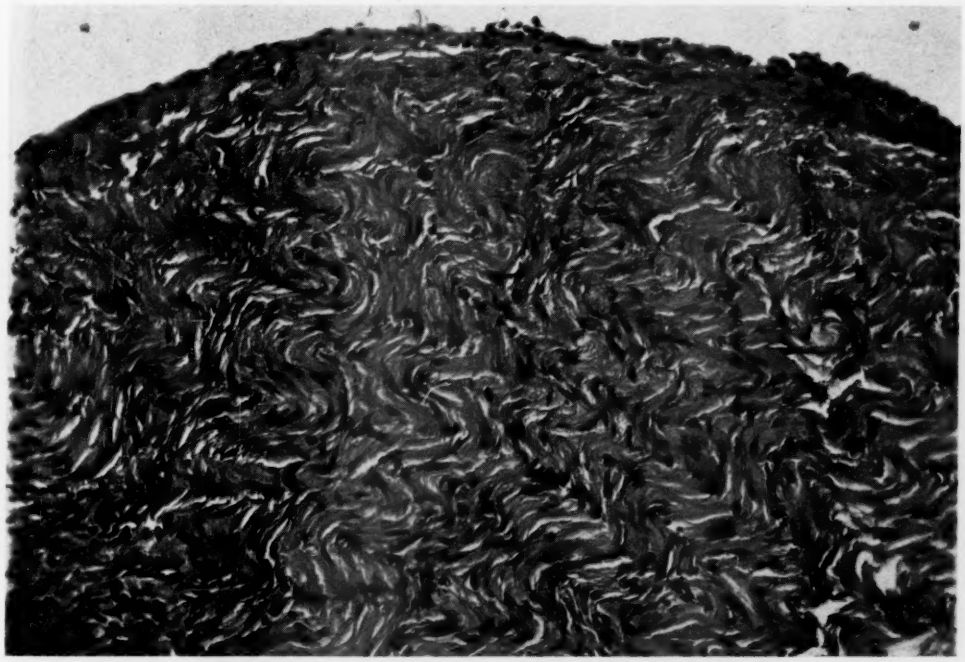

Fig. 2.—Cross section of ovary shown in Fig. 1. The ovarian stroma is normal, but there are absolutely no ovarian follicles. (From Wilkins and Fleischmann: J. Clin. Endocrinol. 4: 357, 1944) (×250.)

This ensemble of congenital malformations found in cases of agenesis of the follicular epithelium indicates that the genetic fault is general, and not limited to the urogenital fold. This distinguishes it from malformations of the Müllerian ducts, in which the defects are usually confined to the urogenital fold. The significance of this will be discussed later.

Congenital Anomalies of the Müllerian Ducts and Associated Malformations

The next group includes cases in which the chief lesion in the reproductive organs is in the Müllerian ducts. In some instances, the associated lesions are more important than the defect in the reproductive organs. In this group, we are merely citing a few typical defects, illustrating the embryologic associations as we have found them.

Bicornate uterus; associated lesions, extrophy of the bladder; separation of symphysis pubis.—The patient was a woman 36 years old, who complained of an extrophy of the bladder. The usual picture was present, the bladder being

entirely exposed on the anterior abdominal wall, the anterior bladder wall being absent, the ureters opening externally and causing a continual leakage of urine on the anterior abdominal wall. The symphysis pubis was separated widely. The left ureter and kidney were normal; the right ureter and kidney pelvis were widely dilated, forming a hydronephrotic mass in the right flank, which secreted only a trace of diorast in sixty minutes.

The lesion in the reproductive organs consisted of a bicornate uterus.

The treatment in this case consisted of implantation of both ureters into the rectosigmoid, performed in 1942. This eliminated the urinary incontinence, and enabled the skin to cover the bladder almost completely. The bicornate uterus was causing no symptoms, and was not disturbed.

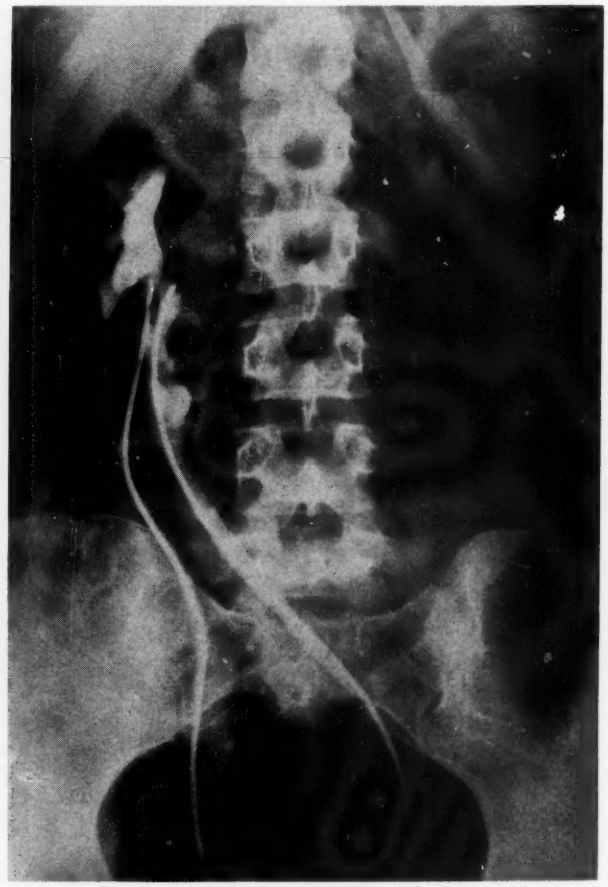

Fig. 3.—Absence of uterus and vagina, associated with crossed unfused ectopy of left kidney.

Absence of uterus; associated lesion; crossed unfused ectopy of left kidney.—Miss J. W., a 21-year-old college student, had complete absence of the vagina and uterus, due to nonunion of the Müllerian ducts. The urinary lesion consisted of crossed, unfused ectopy of the left kidney. The urethra and bladder were normal. The ureteral orifices and trigone were normal. The right ureter followed its usual course to the right kidney, which was normal in every particular. The left ureter crossed the pelvis in front of the sacral promontory and led to a low left kidney which was situated below the right kidney in the right flank, and seemed to be completely separate from it. This is a rather rare urinary malformation (Fig. 3).

The treatment in this case was construction of the vagina. The urinary situation was causing no symptoms, and was not disturbed.

Absence of vagina and uterus; absence of right kidney; ectopic right ovary. —Miss B., a young woman 21 years old, was seen in the Women's Hospital in 1940. She had no vagina and no uterus. She was admitted to the hospital be-

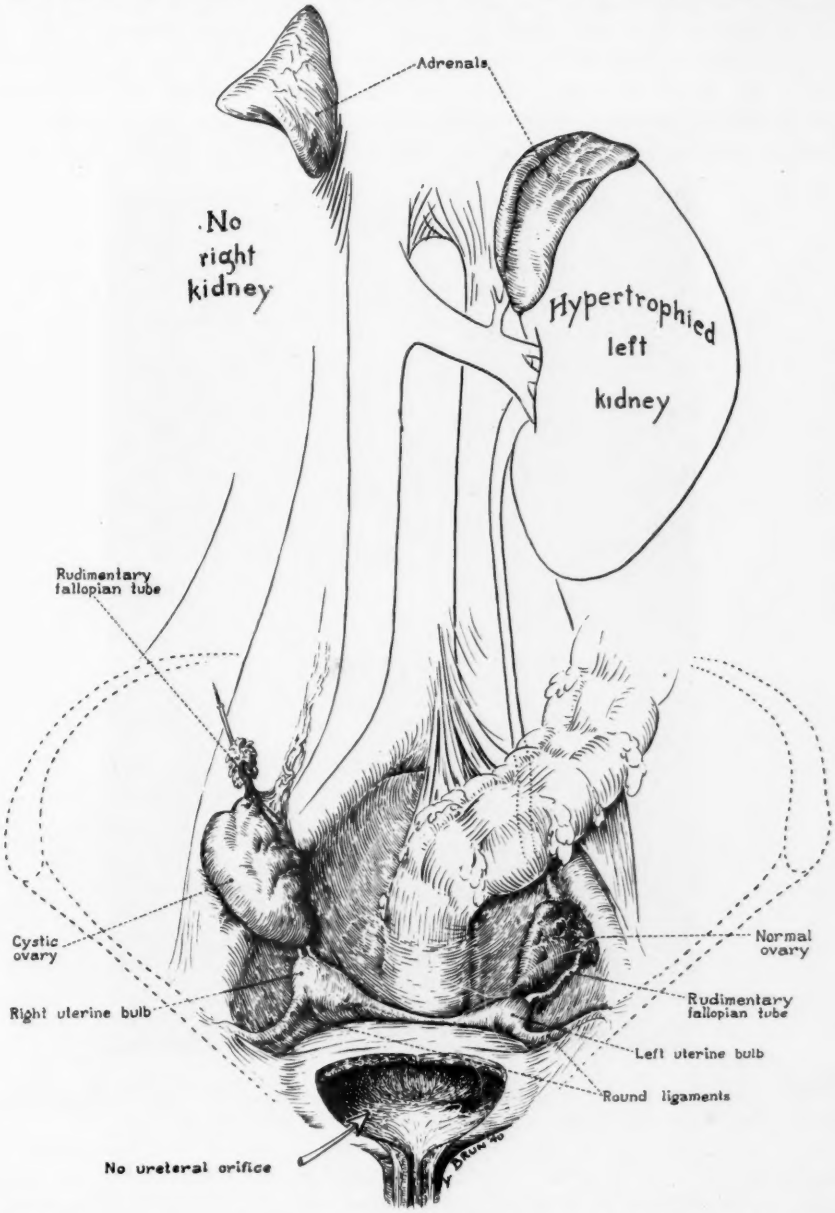

Fig. 4.—Absence of vagina and uterus, associated with agenesis of right kidney and ectopic right ovary. (From L. R. Wharton, Gynecology, Including Female Urology. Philadelphia, 1943, W. B. Saunders Co.

cause of recurrent appendicitis as a patient of Dr. Allen Deckert. The condition of the genitourinary organs is shown in Fig. 4. The right kidney and ureter were completely absent. The right ovary was enlarged, ectopic, lying in the right iliac fossa. It was cystic. The Müllerian ducts presented the typical

picture seen in these lesions. The Fallopian tubes were present, rather rudimentary, with patulous fimbriae. Their mesial ends were separated from each other by a space of about 5 cm., ending in small bulbs. There was no vagina.

The treatment was appendectomy; the patient did not wish to have a vagina constructed.

Absence of vagina and uterus; absence of right kidney; solitary left ectopic kidney in sacral hollow; bilateral undescended ovary; dermoid cyst of right ovary; papillary cystadenoma of left ovary; situs transversus of large intestine. —Miss L. B., aged 23 years, was a clerk for the Federal Government. Her general health had been excellent. Except for the amenorrhea, the first symptom had been a palpable abdominal mass, first noted by the patient herself in 1940,

Fig. 5.—Absence of vagina and uterus, associated with absence of right kidney; solitary kidney, left, ectopic, in sacral hollow; bilateral undescended ovary; dermoid cyst, right ovary; papillary cystadenoma, left ovary; situs transversus, large intestine.

when she was 17 years old. At that time, she was admitted to a hospital in Pineville, La., where the ovarian masses and the appendix were removed. The right ovary contained a dermoid cyst 6 cm. in diameter; arising from the left ovary was a papillary cystadenoma 14 cm. in diameter. The sigmoid and descending colon lay in the right half of the abdomen, and the appendix and ileocecal valve in the right upper quadrant. At that operation, the procedures were bilateral oophorectomy and appendectomy.

After this, three unsuccessful attempts were made to construct the vagina. Fig. 5 shows the location of the solitary ectopic kidney. The ureter swings a little to the left as it crosses the cul-de-sac of Douglas. The surgical treatment was construction of the vagina. In this vaginal dissection, there was no plane of cleavage, and almost every centimeter of space had to be cut by sharp dissection to separate the rectal and bladder walls. Also, the location of the ureter gave us some concern as our dissection approached the cul-de-sac of Douglas. The vagina was lined by Thiersch grafts, all of which were successful. The result of the plastic operation was excellent.

Fig. 6.—Solitary ectopic kidney in a young woman 21 years of age, with absence of vagina and uterus.

Absence of vagina and uterus; absence of left kidney; solitary ectopic right kidney.—Miss J. L., aged 21 years, was operated upon, apparently for "appendicitis," in 1942. She had had recurring monthly pain in the lower abdomen, especially in the right iliac fossa. At operation, the congenital malformation was discovered—absence of uterus and vagina. Her amenorrhea had been attributed to an imperforate hymen. Also, at this operation, the solitary ectopic kidney was discovered.

In May, 1946, she was admitted to the Women's Clinic, and was referred to me by Dr. TeLinde. The gynecologic anomaly had begun to make an introvert out of the young woman. Physically, she was perfectly normal, except for the anomalies in the genitourinary system. The breasts, secondary sex

features, and external genitals were normal. The vagina was represented by a depression 2 cm. deep. Fig. 6 shows the solitary ectopic right kidney, lying in the sacral hollow, with the calyces pointed toward the right iliac fossa. The right ureteropelvic junction is a little to the left of the midline, just above the coccyx, and then crosses the pelvic floor to reach the right half of the bladder. Cystoscopy showed the left ureteral mound and left ureteral orifice to be absent; the right ureteral orifice was normally situated and functioning normally.

At operation (May 21, 1946) a vagina was constructed, using our technique and Thiersch grafts.

Absence of vagina and uterus; horseshoe kidney.—This patient was seen several years ago, and a vagina was successfully made. Unfortunately, the roentgen films were destroyed in accordance with the regulations of the Fire Department.

Vulvovaginal anus with malformation of right kidney and ureter.—Mrs. L., 32 years of age, complained of habitual abortion. She had four pregnancies, none of which she carried beyond the third month.

The author first saw this patient ten years ago, when she complained of rectal incontinence. This was due to the vulvovaginal anus, the anal orifice being situated just within the vaginal orifice. There was no sphincter around the vaginal opening of the rectum, and the patient was completely incontinent, except when constipated. The reproductive and intestinal tracts were otherwise normal.

A routine urologic study revealed the very rare anomaly shown in Fig. 7. Repeated urograms have failed to show the exact extent of division of the upper urinary tract. The kidney pelvis is divided completely into at least two, and probably three or four parts.

Discussion

Agenesis of Ovarian Follicular Epithelium.—We have already mentioned the pathologic features of the ovary in this disorder, and have listed the genetic faults that have been found associated with it. In addition, this condition suggests several other considerations, among which are the *origin of the germ cells, the nature of the genetic fault,* and the *bearing of this condition on the differentiation of sex.*

Ovarian Agenesis and the Origin of Germ Cells.—These cases possibly have some bearing on theories concerning the origin of germ cells. According to one theory, the germ cells originate in the urogenital fold along with the stroma of the ovary, the Müllerian ducts, and the Wolffian bodies and ducts. According to another theory, they have a much earlier origin in the yolk sac, whence they migrate at an early date to the urogenital fold. There they collect to form the sex cells of the gonad. In the forthcoming number of the *Contributions to Embryology,* Witschi traces the migration of the germ cells to their ultimate home in the gonadal folds.

The cases of ovarian agenesis, which we have just described, seem to lend support to the second theory recently espoused by Witschi. In these cases, there is a complete agenesis of the follicular epithelium of the ovary, without any other malformation of the genitourinary organs. In the 40 or 50 cases reported in the literature, Wilkins and Fleischmann[7, 12] have yet to note an instance of double uterus, absence of the vagina, or ectopic kidney, lesions which are commonly associated in congenital defects of the urogenital folds. The absence of

such associated urogenital malformations would therefore suggest that the genetic fault lies elsewhere, probably in primordia of the germ cells, and is effective before they migrate to the gonadal folds. Corner[13] shares this opinion with the author. This would suggest that the germ cells do not originate in the urogenital folds.

The Nature of the Genetic Fault in Absence of Follicular Epithelium.—The malformations associated with this syndrome are so diverse that it is impossible to suppose that they are the result of a fault localized in a single primordium.

Fig. 7.—Vulvovaginal anus with ectopic divided right kidney, and divided ureter. There are at least two, and probably four divisions of this kidney.

This distinguishes the syndrome basically from the simpler defects of the urogenital fold, which are not very frequently accompanied by remote malformations. It also supports the views expressed years ago by Nagel, Guizzetti, Pariset and others, that congenital faults of the ovaries are likely to be associated with extensive general genetic deformities. The only explanation of such fundamental and widely scattered anomalies is that the germ plasm is generally defective, or, as Streeter would say, they are "bad eggs."

Ovarian Agenesis and the Differentiation of Sex.—In these cases, the fetuses developed the female features normally, even though there was no ovarian

follicular epithelium. In other words, the fetus had no functioning gonad; in spite of that, sex seemed to be differentiated normally, the female organs developed and the male organs retrogressed as they should in a normal female fetus. Wilkins and Fleischmann have posed the interesting question as to what controlled this sex differentiation and development in these cases.

It seems that the above cases prove that sex differentiation of the female is not controlled by the gonad of the fetus. The differentiation and development of the sexual apparatus may be initiated and controlled entirely by the chromosome constitution of the fetus, established at the time of fertilization. The maternal hormones may also play a part. This makes one wonder, as Wilkins and Fleischmann suggest, what would happen in a similar situation to a male fetus without any testicular epithelium. This question cannot yet be answered because no such case has yet been reported, as far as I know. These are complicated problems that are best left to the embryologists.

Malformations of the Müllerian Ducts.—Associated with this group of malformations, I generally find other lesions of the urogenital fold, and occasionally defects in the cloaca, bony pelvis, and intestinal tract; all of these organs are closely related in their development. Practically any variety of anomaly of the urinary tract may occur; I have listed horseshoe kidney, crossed ectopy, solitary ectopic kidney, absence of kidney, exstrophy of the bladder, and double ureter and kidney. Vulvovaginal anus and double kidney and ureter were associated in one instance.

The association of genital with urinary anomalies has long been an established fact. Thus, in 1923, Eismayer[3] reported that the homologous kidney was missing in every case of ovarian agenesis that he found in the literature. In 1944, on the basis of autopsy studies, Nation[4] found that 44 per cent of women with absence of one kidney had developmental defects in the reproductive organs. Clinically, these observations have been repeated so many times that it seems superfluous to state again that in every case of congenital malformation of either the genital or urinary tract in either men or women, the whole genitourinary system is to be studied.

Finally, I am forced to wonder whether solitary ectopic kidney is as rare as the literature would lead one to suppose. Thus, in 1944, Lowsley and Menning[5] reported a case of solitary ectopic kidney, stating that theirs was the thirty-sixth case to be reported in the literature. I wonder whether this rarity is not more apparent than real, although I do not mean to infer that it is a common finding. I am herewith reporting a case personally observed, and am quite sure that my associates on the gynecologic and urologic staffs have seen half a dozen more in the last few years. Miller and co-workers[6] and Brady[8] each reported a case in 1945, in discussing methods of constructing the vagina.

It is not only scientific interest, however, which should compel one to make complete examinations of the whole genitourinary system in these cases. In 1944, Lowsley and Kirwin[11] quoted Thompson-Walker to the effect that in 18 recorded instances, solitary kidneys had been removed surgically, always followed by death from uremia. In several of the cases of ectopic kidney which we are reporting, these unusual masses were first discovered by surgical explora-

tion rather than by intravenous urography and adequate preoperative genitourinary investigation. In view of these data, the need of adequate preoperative urologic study can hardly be overstressed in patients with congenital malformations of the reproductive organs or with unusual pelvic or abdominal masses.

References

1. Ogden, H. D., and Maltry, E.: J. Urol. **44**: 13, 1940.
2. Stevens, A. R.: J. Urol. **37**: 610, 1937.
3. Eismayer, G.: Ztschr. f. Urol. Chir. **11**: 191, 1923.
4. Nation, E. F.: Surg., Gynec. & Obst. **79**: 175, 1944.
5. Lowsley, O. S., and Menning, J. H.: J. Urol. **51**: 117, 1944.
6. Miller, N. F., Willson, J. R., and Collins, J.: Am. J. Obst. & Gynec. **50**: 735, 1945.
7. Wilkins, L., and Fleischmann, W.: J. Clin. Endocrinol. **4**: 306, 1944.
8. Brady, Leo: Ann. Surg. **121**: 518, 1945.
9. Thompson, G. J., and Pace, J. M.: Surg., Gynec. & Obst. **64**: 935, 1937.
10. Witschi, E.: To appear in Contrib. Embryol. Carnegie Inst. of Wash.
11. Lowsley, O. S., and Kirwin, T. J.: Clinical Urology, ed. 2, Baltimore, 1944, Williams and Wilkins Co., Vols. 1 and 2.
12. Wilkins, L., and Fleischmann, W.: J. Clin. Endocrinol. **4**: 357, 1944.
13. Corner, G. W.: Personal communication.

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Discussion

DR. HOUSTON S. EVERETT, Baltimore, Md.—In pointing out the coincidental occurrence of gross developmental anomalies in the genital and urinary tracts, Dr. Wharton has brought further evidence to bear upon the advisability of gynecologists and obstetricians being urologically minded.

Anomalies of the bladder and urethra in the female are rare, but anomalies of the upper urinary tracts occur very frequently and are of many varieties. Dees at the Duke University Hospital found anomalies of the kidneys or ureters in 135, or 9.6 per cent, of 1,410 consecutive patients subjected to pyelographic study. Eighty-six, or 73.7 per cent, of these anomalies were found in female patients. Gutierrez has stated that, in his experience, 40 per cent of all pathologic conditions of the kidneys and ureters are due to congenital anomalies.

As pointed out by Dr. Wharton, such anomalies may occur in individuals presenting gross anomalous development of the genitals, but they are found much more frequently in women with anatomically normal reproductive organs. The former group presents no points of interest for the obstetricians, since the individuals in it are incapable of reproducing. In the latter group, however, are found individuals who present points of interest in the obstetric as well as the gynecologic fields. Some of these patients may be enumerated as follows:

1. The anomalous kidney is more prone to disease than the normally developed one. It is therefore more likely to give rise to serious difficulties such as pyelonephritis complicating pregnancy.

2. The ectopic pelvic kidney, whether of the single or fused variety, may be mistaken on pelvic examination for an adnexal mass or a uterine tumor.

3. Such pelvic kidneys may cause dystocia. Six such cases were presented before this Society by Cragin in 1898, and a number of others have been added since. At least two cases, one by McGown and one by Ocherblad and Carlson, have been reported in which injury to an ectopic kidney from compression during labor has resulted in death from renal failure.

Finally, a few years ago we had the opportunity of following during pregnancy a patient with a fused kidney lying entirely within the pelvic cavity. To avoid the possible complications just mentioned, the patient was delivered by cesarean section. The point of major interest was that excretory pyelograms made every few weeks throughout the pregnancy revealed that no evidence of hydroureteronephrosis developed. As the ureters and pelves lay

entirely below the pelvic brim, they were not subjected to compression between the brim and the enlarging uterus, thus demonstrating the importance of the mechanical factor of compression in the causation of the so-called physiologic dilatation of the pelves and ureters of normally placed kidneys during pregnancy.

DR. LOUIS E. PHANEUF, Boston, Mass.—The work of Albright, Wilkins, and Fleischmann has brought out the fact that in some cases, so-called ovarian failure may be due to agenesis or lack of follicular epithelium, whereas prior to their work ovarian failure was usually ascribed to lack of normal gonadotropic stimulation of the ovaries. Rudimentary ovaries are found associated with the partial or complete lack of follicular epithelium. As might be expected, the underdevelopment of the external genitals, the vagina, the uterus, and the uterine tubes is a concomitant of agenesis of the follicular epithelium of the ovary. Dr. Wharton points out that partial agenesis of the follicular epithelium of the ovary, where ovarian follicles, although decreased, though no entirely lacking, may account for some cases of oligomenorrhea in certain individuals who menstruate once or twice a year. If this way of thinking is acceptable, it explains the uselessness of administering gonadotropic therapy in such cases. It is brought out by the essayist that the various congenital malformations in certain persons affected by agenesis of the follicular epithelium, indicate that the genetic disturbance is general and not limited to the urogenital fold, as in the case of Müllerian duct malformations.

Dr. Wharton reports from his own experience the cases of six women with congenital anomalies of the Müllerian ducts and associated malformations. (1) Bicornate uterus in association with exstrophy of the bladder and separation of the symphysis pubis; (2) absence of the uterus with crossed unfused ectopy of the left kidney; (3) absence of the vagina and the uterus associated with absence of the right kidney and ectopic right ovary; (4) absence of the vagina and the uterus, absence of the right kidney, ectopic solitary left kidney in the sacral hollow, bilateral undescended ovaries, dermoid cyst of the right ovary, papillary cystadenoma of the left ovary, and situs transversus of the large intestine; (5) absence of the vagina and the uterus with absence of the left kidney and solitary ectopic right kidney; and (6) vulvovaginal anus with malformation of the right kidney and ureter.

It is obvious from the foregoing that complete urologic studies are essential in the examination of women with congenital defects of the reproductive organs. The modern methods of investigation have greatly simplified this problem. The most common lesion of the Müllerian system for which treatment may be applied is congenital absence of the vagina. The formation of an artificial vagina by Dr. Wharton's method is readily accomplished and is devoid of any great risk. From Sept. 9, 1943, to Jan. 31, 1944, I have operated on three young women by this procedure.

A few years ago, in my office, I saw a young woman who had complete absence of the vagina and uterus. She was referred to my clinic at the New England Medical Center for laboratory and x-ray studies. Within a few months, she brought three other young women with the same affliction. They ranged in age from 17 to 20 years. The mothers of these four girls were sisters, and two patients in each group were also sisters. They were advised to have artificial vaginas constructed when they contemplated marriage.

Dr. Wharton concludes his paper by stating—"In view of these data, the need of adequate preoperative urologic study can hardly be overstressed in patients with congenital malformations of the reproductive organs or with unusual pelvic or abdominal masses." This statement cannot be too strongly emphasized.

DR. ARTHUR H. CURTIS, Chicago, Ill.—I wish to call attention to a clinical observation which has been very helpful to me at the time of operation. If one notes congenital anomalies on the external surface of the body, it is my experience that we shall encounter congenital deviations from the normal within the abdominal cavity, such as Jackson's membranes, mechanical appendicitis, double uterus, and congenital convolutions of the tubes. Often, we are thus forewarned that we should look for a Meckel's diverticulum or urinary tract anomalies.

Among external abnormalities which may arouse suspicion of internal defects are unusual length of distance from the symphysis to the navel, supernumerary nipples, or moles and axillary breast tissue. From the perineal aspect, many deviations are suggestive, such as increased distance of the anus from the examining table, anomalies in the distance between the anus and the vagina, deviations in conformation of the perineum, and distortions and malformations of the external genitals, including increased distance between the meatus and the clitoris.

DR. WHARTON (Closing).—Dr. Everett's discussion brings out the point that many of these women have no obstetric complications. The last one I saw, however, came to me because of habitual abortion. We do not know the cause of that, whether there might be some type of urinary malformation or not. She has some small myomas in addition. The fact that a person has an ectopic kidney may lead to trouble in constructing the vagina. The ureter runs across the pelvic floor, and, if there is no point of cleavage, you might cause an accidental injury in that ureter. So that, in a solitary ectopic kidney you have to watch out for the ureter.

LIFE AND WORKS OF ROBERT MEYER*†

EMIL NOVAK, M.D., BALTIMORE, MD.

ROBERT MEYER was himself not, except in the earlier years of his career, a clinician, and yet there are few, if any, whose scientific contributions have been of greater importance to the clinical gynecology and obstetrics of our times than have been those which he has made. In the field of gynecologic pathology, he has been *facile princeps* for the past generation or more, with also to his credit many important contributions in the field of reproductive endocrinology. Throughout his professional career he has maintained a continuing interest in embryologic research, and some of his contributions in this field have been of monumental importance. Indeed, it is likely that his greatness as a pathologist is due in no small measure to his profound knowledge of embryology, and he himself has constantly emphasized the indispensability of the latter in the elucidation of many pathologic problems.

While a product of the German school in the heyday of its glory, Meyer's sunset years have been spent in our own country, thanks to the exclusiveness of the Hitlerian regime, now so ingloriously ended. He is now a proud American citizen, he has had many American students, he has through his writings instructed and inspired all of our growing American school of gynecologic pathologists, and he is an Honorary Fellow of this Society, as well as of numerous other organizations in this country. In his later years he has belonged to us, and it seems fitting that in our archives there should be preserved some record of the life and accomplishments of this outstanding personality in the history of our specialty.

So far as I know, none but the briefest and most inadequate biographical accounts are available in the country of his birth, and he himself has been too modest to write the autobiography which many far lesser men in our own profession have felt that the world expected of them. Many of us who, like myself, enjoy his friendship, and who are familiar with his scientific attainments, are painfully lacking in knowledge of his background, his early life and education, the forces which influenced him at various phases of his career, his avocations—in short, of all those human details which, to many, are a more illuminating record of a man's career than a cold recital of his purely professional accomplishments.

For most of such details which I have included in this sketch, I have had to assault Dr. Meyer's well-known modesty and reticence and dig them from the reluctant storehouse of his own memory of the happenings in his life. His reward must come not only from my own appreciation, but from that of many friends and admirers who will undoubtedly be glad to learn something of the

*An address delivered at the Sixty-Ninth Annual Meeting of American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

†For lack of space, only a portion of this address can be included in our pages. The complete article may be found in the Society's Volume of Transactions for 1946, and in the author's reprints.

purely personal characteristics of one who is perhaps known to them, as he will surely be known to posterity, as one of the great figures in the history of our specialty. For additional information and reminiscences of Dr. Meyer, I am indebted to some of his former American students, as well as a number of German friends who preceded or followed him in expatriation from their native land.

In spite of the fact that, as he tells me, Dr. Meyer has never kept a diary and never made a point of preserving letters, his still remarkable memory yields many interesting and illuminating details of his early life. He was born in Hannover on Jan. 11, 1864, so that at this writing he is more than 82 years old. He remembers his grandfather, who was more than 74 years old when Robert was born. He had already retired from his business, which was that of banking, and had become seriously interested in the age-old effort to manufacture diamonds artificially. Meyer describes his grandmother as a woman of extraordinary charm, who, in spite of her age and the crippling ravages of arthritis deformans, completely dominated her family of eight children. In addition, and this Robert remembered well, she still knew how to bake wonderful cookies for no less than thirty grandchildren.

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After passing what he calls the most difficult examination of his life, Meyer was ready to follow his older brother to the University at Leipzig. Soon after that his brother became ill, and died shortly of a brain tumor.

It was at Leipzig that Meyer came under the influence of Wilhelm His, with whom he began his studies in anatomy, histology, and embryology. At the Carnegie Institute of Embryology in Baltimore, one can today find a collection of His's own slides, donated by Robert Meyer a number of years ago. In Leipzig, too, he learned to know Thiersch, famous not only because of his transplantation of skin, but also because of his caustic wit. A story about Thiersch concerns King Albert of Saxony, who expressed a wish to witness an amputation. After dextrously amputating the limb, Thiersch saluted the monarch with his saw and then sarcastically said, "Does your Majesty wish the other leg also?"

During the summer of 1884, Meyer studied at Heidelberg, taking comparative anatomy under Gegenbauer and physics under Bunsen. He says that these two great teachers kept him so busy he had time for little else, but this may be questioned, since at about this time he became engaged to his cousin, three years younger than himself, and the daughter of his mother's brother. However, they were not married until six years later. At the close of the summer he proceeded to Strassburg, which had become a German town at the close of the Franco-German war in 1871. There he came under the tutelage of a remarkable group of men. Among them were Gustav Schwalbe, a student of the great Ernst Haeckel; the physicist Kundt who, as Meyer says, experimented so infallibly, and the pathologist von Recklinghausen, who had been the very first assistant of the great Virchow himself. From von Recklinghausen, who in 1863 had discovered the migration of the blood cells in inflammation, and who had also in the same year detected bacteria in tissues,

he learned the fundamentals of pathology, the art of dissection, and the technique of cutting sections by hand, as well as staining them by the natural dyestuffs then available, cochenille and carmine. Although interested in the subject, at this time Meyer did not have any plans or ambition to become a pathologist himself.

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The most brilliant of the Strassburg teachers was the internist, Adolf Kussmaul, who had been a country doctor, but who became such a wonderful diagnostician that when he retired in 1887, von Recklinghausen could say of him that not once at postmortem was he able to reverse Kussmaul's diagnosis. Kussmaul used to complain that "now that we have the thermometer, doctors have forgotten how to diagnose by feeling the pulse." How familiar this sounds today, when a similar plaint is so often heard that the high development of laboratory methods has led doctors to forget the value of the five senses in diagnosis.

The gynecologist and obstetrician at Strassburg was Wilhelm Alexander Freund, famous because he had performed the first hysterectomy for cancer of the corpus uteri in 1878 on a patient whom he could exhibit eighteen years later before the German Gynecological Society at its meeting in Breslau. And yet his pride in this success was less than his resentment that there had been no great acclaim of his work on parametrial inflammatory disease, a type of mental reaction not uncommon among authors and investigators. He is described as a born teacher, whose large lucid eyes, as Meyer remembers, literally illuminated the audience and held it spellbound. Of the remaining Strassburg teachers, Meyer recalls also Heinrich Bayer, who taught theoretical obstetrics, and who wrote on pelvic anatomy and the development of the female sex organs.

On his first day in Strassburg, which happened to be the anniversary of the University, Meyer had been fortunate in meeting a freshman, Curt Neugebauer, who helped him greatly in making his plans, and with whom he formed a close friendship, continuing to the present day. It was in Strassburg also that he fulfilled his military service (1886), and he found this a not at all disagreeable interruption of his studies, although marred by an accident in the form of a fracture of the malleolus. However, as he slyly remarks, this yielded him a pension of nine marks monthly for twenty years. As another instance of high finance, on two occasions (1887 and 1888) he led a party of four students on tours of Italy, since he alone spoke Italian, the total expenses of these regal tours amounting to one hundred marks ($24) per person. He had achieved considerable distinction as a singer, and in Strassburg he became the leader of the tenor section in the choir of the Academy of Music.

Among his fellow students were not a few whose names have helped to make medical history. For example, there was Ludwig Aschoff, who later became the famous pathologist of Freiburg, a man of joyful temperament and an eloquent teacher who attracted students from many countries, especially Japan. He and Aschoff became fast friends at Strassburg, and this friendship continued throughout their later lives. Meyer still prizes a small bronze relief of Aschoff presented to the latter by his friends on his seventieth birthday. Another student was August Wassermann, known for his work in syphilis,

and still another Wilhelm His the younger, the discoverer of the His bundle in the heart. Yet another was the gifted Robert Müllerheim, who later demonstrated the first roentgenograms of the living child in utero. He became the assistant of the gynecologist Freund, but Meyer admired him especially because of his love of art, the ancient classicists, and etymology. Meyer saw much of him in later years, when Müllerheim had taken up gynecologic practice in Berlin.

And then came the day of final examinations, and it was with Müllerheim and Neugebauer that Meyer appeared before the examiners. All were passed with flying colors, and were congratulated by Hoppe-Seyler, the dean, the date being Dec. 29, 1888. Shortly afterward they submitted their theses for the doctorate, Meyer's title being "Ein Fall von statischen Reflexkrampf." In the selection of this thesis he was influenced by Professor Tolly, the neurologist.

Meyer had already made plans for his immediate future, and in these he appears to have been largely influenced by Kussmaul, who would often invite students to his home in Strassburg, and who urged that country practice afforded the best opportunity for the young doctor to learn medicine. Meyer had been much impressed, and had already decided to follow this advice. Instead, therefore, of seeking an assistancy, he went to Berlin to study as a "voluntary" at the Krankenhaus am Friedrichshain, becoming interested chiefly in the urological clinic of Fürbringer, who had written an excellent textbook on his specialty. He remained here some months, utilizing the remainder of the year 1889 to learn other things in various fields in preparation for his contemplated work as a country practitioner. It was during this period that he learned to know Robert Koch, the father of formal bacteriology. He describes him as a very serious man, who spoke very little. I can personally endorse this impression, because many years later, when I was a medical student, I had the honor of meeting the great Koch in Baltimore, which he visited during his lecture tour in this country. He impressed me as cold, unmagnetic, and taciturn, and I particularly recall that the hand which I so worshipfully shook had about the same feel as a cold fish.

And now our future great scientist was ready to begin his short career, destined to last four and three-fourths years, as a country doctor. Through a newspaper advertisement which his mother had clipped and sent him, he was led to the village of Dedeleben, a town of 2,100 people, taking over the practice, the house, three horses, buggies, and sleigh of a retiring country doctor.

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Life moved on very agreeably, in spite of the rigors of practice. There were frequent excursions to the Harz mountains, with often calls to distant patients on the way. Meyer was a regular attendant at the regular monthly medical meetings in near-by Halberstadt, a town of 25,000 people. A prominent figure at the meetings was Hans Kehr, later a famous surgeon in Berlin, and even then rapidly achieving distinction in the field of gall bladder surgery. His two large volumes on this subject are well known to surgeons.

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And then, in 1895, came an event which proved to be a turning point for Meyer, since it appears to have deflected the current of his life into the channels of gynecologic pathology. One day, at the home of his uncle, he met a doctor who asked him whether or not he was too busy to serve as "volunteer" in the private clinic of Johann Veit, also professor of gynecology at the University. Veit had written an excellent monograph on tubal pregnancy, and was the editor of the *Handbuch für Gynäkologie* (1897). After his death this office was taken over by Stoeckel, and the Veit-Stoeckel *Handbuch* has remained perhaps the most popular reference work in its field.

Meyer describes Veit as a very genial man, though his geniality was perhaps a bit overaccentuated. In his private clinic he operated with his two regular assistants and Meyer, who, in addition, was put in charge of the pathologic laboratory, a tiny room about the size of a large closet. In these simple quarters began Meyer's career as a pathologist. He still kept up his practice, and for fear of missing professional calls, fitted up a room in his own home as a supplementary laboratory. He had a microscope, and, since he had to be his own technician, he purchased a microtome, soon becoming expert in the preparation of sections and in microscopic diagnosis. He still has some of these early sections, including some through the whole kidney, indicating what a virtuoso he had become.

In about 1896, Johann Veit accepted the chair of obstetrics and gynecology at the University of Leyden, in Holland. Before leaving Berlin he suggested to Meyer that if he were at any time in need of material or of counsel, he consult Carl Ruge, the prosector of the University Gynecological Clinic. At this time Meyer took a course in practical embryology with Oscar Hertwig, who had given the first description of the process of fertilization (in the sea-urchin), and who had written what Meyer calls a wonderfully clear book on general biology, from which he had learned a great deal. He also met Paul Ehrlich, the discoverer of salvarsan.

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Carl Ruge, who now began to play an important part in Meyer's life, had worked under Virchow, and in 1869 had won the University prize for his excellent work on the pathology of the bones. He was born in 1846, the son of a physician, and a nephew of Virchow's wife, who in turn was the daughter of the famous gynecologist, Carl Mayer. After the Franco-German war (1870 to 1871) Ruge became assistant in the University Frauenklinik, and when the clinic acquired its own pathologic institute in 1887, he was advanced to the post of prosector. Like Meyer, he continued as a busy practitioner, but retained his direction of the pathologic institute until 1912, when he was succeeded by Meyer. It is Ruge and Veit, but especially the former, who deserve the credit for the beginnings of gynecologic pathology, while Meyer, the successor of Ruge, later became the recognized world leader in this special field.

It is to Ruge and Veit also that we are indebted for the introduction of biopsy as the only possible means of early and certain recognition of cancer of the cervix (1878) and of curettage as a corresponding diagnostic procedure for

carcinoma of the corpus (1881). Ruge fought valiantly for his views, against which there was much opposition, and he constantly urged that gynecologists make themselves independent of pathologists by becoming pathologists themselves. This idea, after a great many years, appears to be coming to its own, as judged, for example, by the insistence on some knowledge of pathology as one of the requirements for certification by our American Board of Obstetrics and Gynecology. With Ruge, Meyer began a warm friendship which continued for thirty years, and which was strengthened by the marriage of Ruge's daughter with Mrs. Meyer's brother. At this wedding Meyer states that no less than 108 relatives of the Ruges were present.

It was in 1903 that Meyer first made contact with Lubarsch, then the pathologist at the Academy of Medicine in Posen. This first contact was not altogether a pleasant one. Lubarsch was, of course, a highly trained biologist and pathologist, and among other things he had founded the *Ergebnisse der Pathologie,* which he edited until his death in 1933. However, he was an arbitrary, dictatorial, and pugnacious individual, who seemed to stir up trouble wherever he was. One of his pupils, Arthur Stein of New York, had published a paper describing a case in which the diagnosis was carcinoma of the Müllerian epithelium, and Meyer, in a letter to Stein, had taken issue with this diagnosis. Since it was Lubarsch who had really made this diagnosis, Meyer promptly received from the latter an offensive reply, and half an hour later he visited Lubarsch, who happened to be visiting his mother in Berlin. His reception was cool and haughty, but Meyer knew his embryology as few others did, and soon convinced Lubarsch of his error. Eight days later, a letter came from Lubarsch inviting Meyer to write on embryonal failures in female sex organs for the *Ergebnisse,* and one year later a masterly review of the whole subject, comprising 200 printed pages, was in Lubarsch's hand. The pathologists of the country began to ask "Who is Robert Meyer?" At this time he was still a private practitioner, with the same brass plate, reading "Physician and Obstetrician," on the front of his house door.

In March, 1908, Meyer received what he describes as a startling offer, and one which changed the whole current of his life. The great Ernst Bumm, was then the head of the Charité Clinic, and through his assistant, Lippman, Meyer was offered the directorship of Bumm's laboratory, with the title of professor. He was then 44 years old, and he asked for three days to make his decision. At the end of that time the brass plate came down from the front door, and henceforth the busy practitioner with the love for pathology entered academic life as a pathologist.

Bumm, whom Meyer knew as president of the Gynecological Society, was an agreeable chief, and easy to work for. When he was later transferred to the University Clinic on Artillerie-strasse, a Mecca for American gynecologists of a generation ago, Meyer remained on at the Charité for two additional years with Rudolf Franz, Bumm's successor at that clinic. Many of us will remember Franz as perhaps the most skillful operator in Berlin, and a splendid teacher as well. He and Meyer remained fast friends until Franz's death at the prime of his life, as a result, incidentally, of dysgermonoma or seminoma of the testis.

During his Charité days, Meyer, with the enormous amount of material now at his disposal, was increasingly productive. His published works during this comparatively short era included studies on the Wolffian duct, the development of the male genitals, the utriculus prostaticus, the mesonephros and the nephric intermediate blastema, metanephric vestiges in the inguinal region, and congenital abnormalities of the kidney. Throughout all these studies, his deep interest in and his profound knowledge of embryology are clearly manifest. In 1911, he published his comprehensive monograph on embryonal anomalies in general, including those of the male sexual organs, for Lubarsch's *Ergebnisse,* with another comprehensive article on the same general topic the following year in the *Zeitschrift* (1912). In both these works he discussed many fundamental problems in masterly fashion. Among other things he emphasized that Cohnheim's well-known theory of embryonal inclusions as a cause of tumor formation was inadequate, since most such tissue inclusions ripen to normal tissue. He insisted that it is the indifference or immaturity of the embryonal tissue which is essential to tumor formation.

In 1912, Meyer moved over to the Artillerie-strasse clinic with his old chief, Ernst Bumm, becoming the successor of Carl Ruge as prosector of the Pathological Institute. Many of the older Fellows of this Society will have pleasant memories of the courtly and aristocratic Bumm, and of his gifts as a clinician and teacher. Bumm was an artist, and, indeed, had planned to become a painter before he embarked on the study of medicine. Many of us will recall how, with a piece of chalk in each hand, he would stand before the blackboard, and within a few moments produce an astonishingly graphic visualization of the particular point he wished to impress on his audience. His textbook on obstetrics was the best of its day, and, incidentally, he was the royal accoucheur in the prolific household of Kaiser Wilhelm.

And now Meyer began his important series of publications in the field of ovarian tumors, in which he had always been interested. It is probable that his contributions in the study of ovarian tumors are better known, at least in this country, than any of his numerous other activities. In 1914, he wrote on adenoma tubulare malignum, and in 1915 came the paper on carcinoma ovarii folliculoides et cylindromatosum, in which he discussed for the first time the histogenesis of a group of tumors from granulosa cells dating from a very early phase of ovarian development. There soon followed studies of the normal and pathologic anatomy of the medullary cysts and tubules and of the rete ovarii, though these studies were not published until 1920 because of the interruption of World War I.

During the war, Meyer served on the staff of a military hospital in the outskirts of Brussels, his work including not only general and orthopedic surgery, and the treatment of venereal diseases, but also the conduct of the x-ray laboratory. Occasionally he was called upon to escort numbers of insane or venereal patients back to Berlin, these trips giving him an opportunity of visiting his family. However, he had more frequent opportunities of seeing his son, who was stationed on the western front. During the "flu" epidemic of 1918, the son was desperately ill with bilateral pneumonia, and Meyer was

allowed to nurse and care for him during his illness, from which he fortunately recovered, though he later had no recollection of his father's presence.

His scientific work was certainly not forgotten during his absence from his laboratory, because he somehow found time during this period to publish his paper on the histogenesis and classification of ovarian tumors, and another on rare ovarian tumors. In the latter, he describes not only the granulosa-cell type, but also a tumor in a girl of 10 years, belonging to the group to which he later gave the name of dysgerminoma.

Meyer (the bearded officer on the stairs) behind two German princes, chiefs of the Red Cross, at a hospital in Brussels where Meyer was stationed in World War I.

He had little time for reorientation and refamilarizing himself with the literature, for soon after his return Lubarsch, now the pathologist at the University in Berlin, called on him to write the section on "Pathology of the Uterus," and also on hydatidiform mole and chorionepithelioma, for the famous Hencke-Lubarsch work on *Specielle Pathologie,* and to delegate other sections dealing with the female generative organs to whomever he might select, with the exception of the chapter on "Pathology of the Ovaries," previously committed to J. W. Miller. At the same time, he accepted the responsibility for the preparation of a number of chapters for the Veit-Stoeckel *Handbuch* (Vol. VI). These publications did not appear until about ten years later. They cover the whole field exhaustively and authoritatively, so that even today they remain the chief sources of our knowledge of the many subjects covered by Meyer.

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In 1923, he was invited to lecture and to give a course in microscopic pathology in Oslo (Norway), and also in Upsala (Sweden), and he was greatly impressed with these countries and their professions. During all of this time articles flowed from his laboratory and pen, as a glance at his bibliography will show. His sixtieth birthday was recognized by the Berlin Gynecological Society, and on this occasion his chief and friend, Bumm, expressed the Society's congratulations in his characteristically kindly and eloquent manner. At the end of this year Bumm died quite suddenly, and Meyer was called upon to speak at the mass for the dead. The entire clinic was grief-stricken, for Bumm was universally loved and respected, and Meyer felt his loss very keenly.

During the rather long interim before Stoeckel was appointed to succeed Bumm, Meyer gave weekly evening lectures to the clinic assistants, in order to keep up the spirit of the clinic. The new Geheimrath was a striking contrast to his predecessor, being of rather typical, formal Prussian temperament, and lacking the kindliness and geniality of Bumm. However, he was a prodigious worker, and his deep interest in both the patients and the staff won him general respect. He was the editor of both the *Zentralblatt* and the *Zeitschrift,* and later found time to create a new *Zeitschrift,* that for Gynecological Urology, in which his greatest interest lay. Moreover, he was the editor of the third edition of the Veit *Handbuch,* to which he added three large volumes on Gynecological Urology. He is described as being a gifted orator and a splendid teacher. Stoeckel and Meyer, so different in many of their personal characteristics, soon developed much respect and admiration for each other's gifts, and they became fast friends. Contrary to what many have believed, Meyer insists that Stoeckel has never been a member of the Nazi party, though he contributed to it by delivering two little Goebels.

Stoeckel showed his esteem for Meyer in many ways. For example, when Prof. Heller, the pathologist at Kiel, died, Stoeckel proposed Meyer as his successor. However, Lubarsch was chosen, but Meyer was not disappointed, for he preferred his agreeable position in Berlin. His productiveness continued unabated.

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In 1924, Meyer took rather sharp issue with Corner and other American anatomists in their introduction of the term "anovulatory menstruation," holding that only the cyclical physiologic bleeding which is preceded by ovulation and progestational changes in the endometrium should be spoken of as menstruation. In this view he was supported by Schroeder, and he still maintains the viewpoint in his most recent publication, appearing in the January, 1946, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. On the other hand, the American investigators have likewise not receded from their position, and the term as well as the concept of "anovulatory menstruation" seems to have entrenched itself rather securely, at least in this country.

During these years Meyer contributed many abstracts and reviews to the well-known *Berichte ü die gesamte Gynäkologie u Geburtshilfe,* and in 1928 he prepared for this publication a very exhaustive review on the function of the

ovary, especially the corpus luteum. It is a complete storehouse of knowledge of all aspects of the subject up to that time, with a bibliography of about 250 references.

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The year 1930 is an important one in Meyer's life, because it marked the publication of a number of classic papers on special ovarian tumors, the contribution for which he is perhaps best known to American gynecologists. Three papers dealt with the subject of the masculinizing tumors of the ovary, to which he gave the name of arrhenoblastoma, applying this term not to any one stereotyped histologic form, but to a whole series of gradations made possible by the development of such tumors from certain originally male-directed elements in the ovary, the tumors reproducing testicular characteristics with varying degrees of imperfection. He divided this tumor group into a ripe, unripe, and intermediary variety, showing that the so-called testicular adenoma described many years earlier by Ludwig Pick really represents the highly differentiated variety of arrhenoblastoma. He also described in perfect detail the sequence of defeminization and masculinization phenomena produced by these tumors, and regressing after their removal.

In another paper during the same year he described as another definite group the granulosa-cell tumors, a number of which had been previously reported by von Werdt and others, although often confused with tumors of totally different nature and origin. With the granulosa-cell tumors, as with arrhenoblastoma, he gave us a perfect description of the feminizing effects produced at various age epochs. The third important tumor derived from cells dating back to an early undifferentiated phase of gonadal development he designated as a dysgerminoma, with no effect on sex characteristics. This tumor type, the "gross-kerniges or gross-zelliges karzinom" of previous German writers, had for many years been misinterpreted by all pathologists, but Meyer gave us a sharply drawn description of its histogenesis, gross and microscopic characteristics, as well as its clinical implications.

As the fourth member of what he then included as the "special tumors" of the ovary, he delineated the Brenner tumor, previously described but wrongly interpreted, under such designations as oöphoroma folliculare. He also demonstrated that in the cystic form there may be a pseudomucinous transformation of the epithelium, with at times the production of even large pseudomucinous cystadenomas. Most of us would be satisfied to have made even one such contribution, as is represented by Meyer's classical studies on this tumor group, and yet it was only one episode in his productive life as a pathologist.

It was this particular subject which he chose for his address before the American Gynecological Society as its foreign guest in 1931. It was not until the year before, he says, that he began to study English, although he had, of course, a reading familiarity with the medical literature in that language. When the cabled invitation to speak in America came from Dr. Graves, our president of that year, he was quite thrilled, and amusingly states that he and

Mrs. Meyer had a long debate, finally deciding for acceptance. She then reminded him that he ought to cable his acceptance, but he told her that he had already done so on the way home.

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But the steady stream of Meyer's scientific productiveness flowed steadily on. To show the diversity of his interest, he made an exhaustive study of the so-called "myoblasten myoma" of Abrikossoff, arising from a special type of myoblast in the muscles of the throat and mouth regions, as well as the muscle elements of the skin. Again, in papers by himself and by two of his old students, Kaufmann and Aschheim, he reverted to the subject of the proliferative phase of the corpus luteum, the existence of which was doubted by the French pathologist, Moulonguet, with whom an interesting controversy thus took place.

The year 1932 is marked by the beginning of Meyer's monumental study, which was to continue for many years, on the development of the human vagina. This, to my mind, represents perhaps his most important scientific contribution. It was during a period of political turbulence in Berlin that he sought solace in this study of "constitutional embryology," as he likes to call it. For this long and patient study 112 fetuses were cut serially, although in the larger fetuses only the pelvic organs were thus sectioned, while in 14 others special sectioning of various anomalies was done. From this large material he made about 3,000 photomicrographs, which he collected in five large albums which were dedicated to Professor Stoeckel. These were deposited in the library of the University Frauenklinik in Berlin.

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In January of 1934 Meyer's seventieth birthday was honored by an imposing celebration in Berlin. Meyer was presented with a bronze bust of himself, the work of Fritz Klimsch, one of the best sculptors in Germany. The presentation address by Stoeckel expressed the admiration and affection in which Meyer was held in the gynecologic and pathologic worlds. He was the recipient of many congratulatory letters from all parts of the world, including messages from the presidents of the German Gynecological and German Pathological Societies, and the President (Rector) of the University. The latter expressed gratitude for all that Meyer had done and was still doing for the benefit of all connected with the University, from his oldest colleagues down to the youngest students. Stoeckel, in the course of his eloquent address in the presentation of the bronze bust said, "You began as a student and friend of Carl Ruge, who drew the first plough through the virgin soil of pathologic gynecology, but you have completely plowed the soil and planted it, so that hitherto barren stretches have been brought into full bloom, and much new land has been brought under cultivation. You are the creator of gynecologic histology and in this field you have become an uncrowned king, a 'praeceptor mundi.' "

During this time the Nazis were becoming more and more powerful, and also more and more antisemitic, but Meyer was not disturbed in his position

until the end of 1935. And then the man who, less than two years previously on the occasion of his seventieth birthday, had been acclaimed by all his colleagues, was dismissed from his post at the university. Through the intervention of Stoeckel he was allowed to continue unofficially until the end of 1938, without salary, but with permission to retain the fees he earned from his large consulting pathologic practice. Since the latter yielded him no less than 24,000 marks annually, and since his salary had been only 6,000 marks, the financial loss was not so great, especially as his private income jumped to 30,000 marks within the year after his dismissal. But at the end of 1938

Bronze bust presented to Meyer at a celebration on his seventieth birthday.

the Nazi minister of the interior and the minister of education decided, as Meyer laconically states, that the German nation was now antisemitic enough to get along without him. During this trying time Stoeckel was very kind to him. Meyer was now busy with plans for his departure to America, and corresponded with some of his old friends and former students in this country, among them John McKelvey, through whom he was later offered a post at the University of Minnesota. He received permission to leave the country without being put under the quota, and this proved to be an immense advantage, since he got out of the country on almost the last train the very day the war broke

out. Through a friend in the customs, he was able to get out at least a part of his furniture and all of his scientific material.

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He continued his work at the University of Minnesota, with the rank of Associate Professor, until 1944, since which time he has been leading a quiet, but anything but idle, life. He is as intensely interested in work as ever, and at present is engaged in the study of the development of the ureter. He has also been a faithful and invaluable member of our Committee on Ovarian Tumors.

It must interest us all, in viewing the enormous scientific output of this man, to know something as to his methods of work, and I put just this inquiry to him. He tells me that he has always read every possible publication in his immediate fields of embryology, anatomy, biology, and pathology, as well as in many others, and that he made and filed abstracts of them, whether or not they bore on any problem in which he was at the time interested. He destroyed many thousands of these abstracts when he left Berlin, and still has many thousands which he will never use. He wrote all his papers in longhand, often rewriting them three or four times. He says he could not write a paper from beginning to end, but would put down ideas as they occurred to him, these in turn suggesting new ideas as he wrote. Not a single one of his many papers, he says, has been written in good order from start to finish, all being rewritten perhaps several times. How a man who never seems to be in a hurry could accomplish all this is hard to believe.

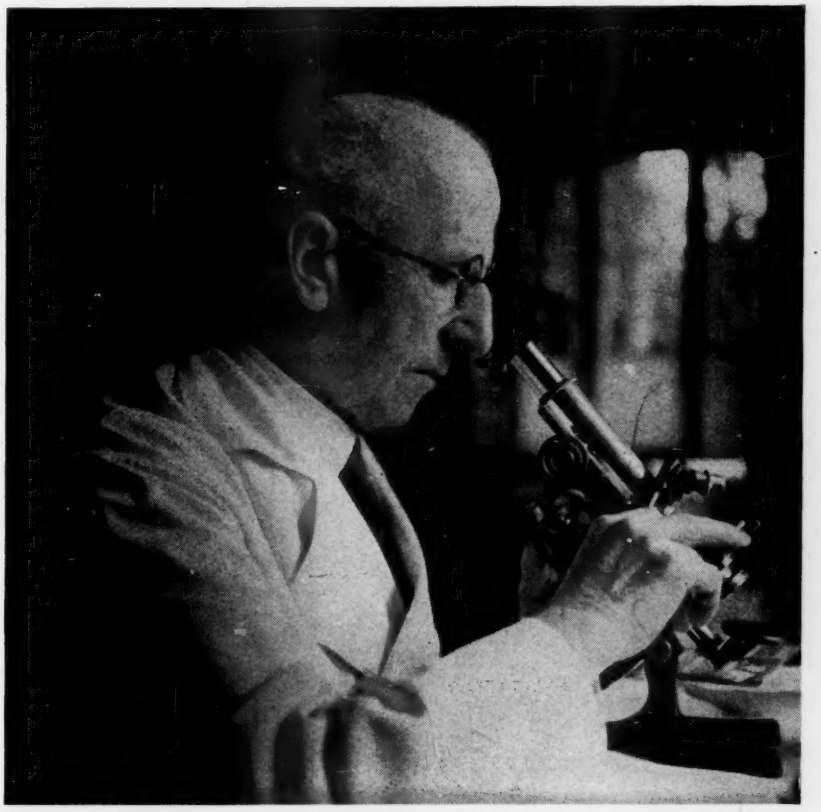
Perhaps his own experience is responsible for his editorial policies during his long career as coeditor of the *Archiv für Gynäkologie,* and departmental editor of the Hencke-Lubarsch *Handbuch der Speciellen Pathologie.* He does not believe in any such thing as editorial standardization, preferring to allow the author all possible individuality of style and presentation, so long as the content of his paper is good.

By some he has been said to be unnecessarily critical in his writings. To be frank, I was inclined to believe this from his writings before I learned to know him. No one could be more modest and unaggressive, and what might seem to some to be arbitrariness is really only the authoritativeness which comes from assured knowledge. He is indeed much more critical of himself than of others, and likes to quote the words of a French scientist, "What I know, I do not know with absolute certainty; but what I do not know, I am entirely ignorant of."

A more complete biography of Robert Meyer would have to include a far fuller review and evaluation of his contributions than has been possible in this comparatively brief account. Furthermore, I have deliberately chosen to devote much of this paper to the human rather than the scientific aspects of his career, because such illuminating side lights, easily forgotten in a few years, should be preserved in our archives, while the scientific publications will remain an important segment of the literature of our specialty for many years to come. I have, however, taken pains to track down his publications as completely as possible, although I am sure there are some omissions in the

bibliography appended to this paper, imposing though it is with its approximately 200 references. This includes only his major publications, and not the innumerable discussions and demonstrations which he gave before many scientific gatherings. Nor does it take cognizance of the scores of important papers by his assistants and students, guided and inspired by Meyer himself.

My personal evaluation would be that his greatest contributions have been in the field of embryology, especially the embryology of the vagina. Perhaps next would be his work with ovarian tumors, especially the "special" group which he, so to speak, put on our gynecologic map. Others, perhaps, would consider of equal or greater importance his numerous contributions to the problem of cancer diagnosis, dating back to his early days with Carl Ruge, who first stressed the value of biopsy and curettage as decisive procedures.



A characteristic picture of Meyer at his microscope.

The endocrinologists, too, would not wish to have us underestimate the fundamental value of his studies of the corpus luteum life cycle or that of the endometrium, and the correlation of the two. And what about his publications on cervical erosions and epidermidization, hydatidiform mole and chorionepithelioma, endometriosis and adenomyosis, the hitherto almost untouched field of nerve tumors of the pelvis, and the elucidation of many types of genital and fetal abnormality? Many of these subjects are described in his contributions to the Handbooks of Veit-Stoeckel and Henke-Lubarsch.

The personal traits which have made his scientific career so rich and full, it seems to me, are his absolute intellectual honesty, his enormous capacity for work, and his rich endowment with that "equanimitas" which our own beloved Osler esteemed so highly.

He has a wonderful sense of humor, and I wish there were time and space to give some examples of the really sparkling wit with which his letters abound. He has this to say in retrospect about his own life. "I have had an exceedingly beautiful life which would be worth while living once more. I have had no sorrows except those which I made myself, and they were unimportant. I have always had the feeling in difficult situations that things would come out well, and they did. I let life approach me, made my decisions, and they were right. I did not seek or apply for any position. I had nobody to ask for recommendation. I was in every way independent. I worked for my own satisfaction. My life, without planning it so, was rectilinear. I have never been an assistant except for one short period, and have never had the ambition to be "privat docent" of pathology or anatomy, as might have been expected of me. I was an autodidact. I had no special plan and no connections when I began to study pathology at an age at which most men are already settled in a career. In retrospect, that course seemed to me quite reasonable at the time I did it, but why I did it, I do not know. It seemed to me important at the time. It happened that it offered me something, and whether or not I was to take full advantage of it, it was the right thing to do."

He has not been embittered by the fact that he was caught up in the savage and costly orgy of Hitlerism which has ruined his Fatherland, both economically and scientifically. He suffered grievous blows in the premature death of his cherished son, and in the loss only two years ago (1944) of his beloved and devoted helpmate of many years, but at no time has he inflicted his sorrow upon his friends. He is spending his sunset years serenely but not idly in a land far from the mother country which cast him off, but which could not rob him of the high position he had already achieved in the world of science. No greater name is inscribed in our roll of Honorary Fellows than that of Robert Meyer.

(A complete bibliography of Professor Meyer's contributions to the medical literature may be found in the Society's Volume of Transactions, and the author's reprints.)

Original Communications

THE OFFICE STUDY OF INFERTILITY*

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A PRACTICAL working procedure for the office study of sterility in the female directs the search for contributing factors into four main directions: (1) mechanical factors, (2) chemical factors, (3) endocrine factors, (4) general factors.

Mechanical factors are those which exist to impede or obstruct the union of the sperm and the ovum. They include the more or less common conditions of cervical strictures and secretions, retroflexed uterus, tubal occlusion. They are discovered in the course of the ordinary gynecologic examination, and with the aid of the insufflation apparatus devised by Rubin. Carbon dioxide in controlled amount and under controlled pressure is passed into the uterine cavity and, in the case of patency, through the Fallopian tubes into the abdominal cavity. Patency is demonstrated by kimographic tracings which, in addition, record the presence or absence of tubal peristalsis, by hearing the gas as it passes from the narrow lumen of the tube into the wider abdominal cavity, by visualizing in the fluoroscope the gas as it has accumulated under the diaphragm, and by the occurrence of shoulder pain. In the case of the badly infected cervix, mechanical factors may be introduced by thick, tenacious, or mucopurulent discharges. This may be seen by the method of Huhner of direct observation of the sperm as obtained from the cervical canal.

Chemical factors in sterility are studied by the method of Huhner and Kurzrock. A chemical imbalance may exist between the normally alkaline cervical secretions, normally acid vagina, and normally alkaline seminal fluid. In addition, infection may introduce chemical disturbances that are definitely destructive to the sperm. Direct observation of this is possible by obtaining postcoital samples for microscopic examination. The pH of cervical and vaginal mucosa may be determined by the use of suitable indicators.

The office investigator will find his endocrine studies limited to two practical and valuable observations. First, the determination of the basal metabolic rate. Litzenberg, in 1937, and many investigators subsequently have pointed out the importance of the thyroid-ovarian association. Definite hypothyroidism, and the less definite subclinical hypothyroidism, are important factors in sterility Second, the determination of ovulation. The introduction of the aspiration curette by Novak has made this an office procedure. Endometrial biopsies obtained just before or in the first few hours of menstruation will show the typical

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secretory endometrium showing the luteinizing effect of the ovary, and thus, by inference, the occurrence of ovulation.

General factors in sterility are emphasized by Meaker. By them are meant such conditions as anemia, foci of infection in tonsils, teeth, etc., pyelitis, nephritis, tuberculosis, etc. These are determined in the course of routine physical and laboratory examinations.

This series of cases under consideration consists of 210 women studied by all means available to us and according to the plan outlined. They are unselected, with no effort to evaluate any particular type of treatment. An attempt has been made to answer the questions: "What have we to offer the woman who complains of infertility for any reason whatsoever? How many of them will eventually succeed in attaining normal, viable offspring?" The series consists of cases in whom conception is obviously impossible, such as the congenitally abnormal and the surgically crippled. It includes cases incompletely studied and treated, due to change of residence, wartime dislocation, etc. In other words, it is the over-all picture of the kind of patient seen, the kind of treatment undertaken, and the kind of results obtained in our offices.

TABLE I. AGE OF PATIENTS

AGE (YEARS)	NO. OF CASES
20-25	25
26-30	67
31-35	55
36-40	23

It would appear that the woman's greatest desire for offspring occurs within the age group 25 to 30 years, and, similarly, her alarm at her inability to conceive brings her to the physician most often at that time. Under the stimulus of an even greater urgency, an almost equal number will appear between the ages 30 to 35 years. Five successful pregnancies occurred after the age of 36 years. The age of the husband was in line with the wife. In the group of cases in which pregnancy was successful, the oldest recorded age for the husband was 47 years; in those not successful, the oldest was 53 years.

TABLE II. YEARS MARRIED BEFORE SEEKING MEDICAL ADVICE

YEARS	CASES	PER CENT
1-5	102	53
6-10	69	30
11-15	22	11

Fifty-three per cent of infertile women will seek medical advice within one to five years of married life. On the other hand, 63 per cent of the women who subsequently become pregnant had consulted physicians by the time they were married five years or sooner. This would seem to confirm the impression that the longstanding, untreated case of sterility has the least satisfactory response when treatment is undertaken.

TABLE III. YEARS WITHOUT CONTRACEPTION

NO. OF YEARS	NO. OF CASES	PER CENT
1-2	64	33
2-3	27	14
3-4	39	20
4-10	62	32

The same thing is shown in principle when the number of years without contraception is considered. Although one-third of all women had consulted a physician not later than two years without contraception, 50 per cent of the cases that subsequently became pregnant had been not longer than two years without contraception. In this series, no case was considered unless without contraception of any type for at least one year.

TABLE IV. PREVIOUS PREGNANCIES

TYPE	NO. CASES
No pregnancies	153
Abortions	
Induced	3
Tubal	3
Spontaneous	27
Term	
Stillborn	5
Living	11

Of the 210 women studied, 153 had had no previous pregnancies; 49 were secondarily sterile inasmuch as previous pregnancies had existed. The record for these pregnancies was not good, however, since they represented only 11 living children, 30 had ended in abortions of which three had been induced, five were stillborn, and three were tubal pregnancies. Of the women who subsequently became pregnant under treatment, only two had had living children, one had had a full-term stillbirth, eleven had had abortions, and one had had an ectopic pregnancy.

Mechanical and Chemical Factors

Mechanical and chemical factors in the sterility of this group were found or suspected on the basis of: (1) history; (2) chemical tests such as the use of indicators in the vagina and cervix; (3) detailed examination of the reproductive tract such as the use of the sound, observation of the cervix and its secretions; (4) palpation of the uterus and, sometimes, of the tubes; (5) the Huhner test which is an indicator of both chemical and mechanical abnormalities; (6) tubal insufflation as devised by Rubin; (7) lipiodol and x-ray studies of the tubes and uterus.

Although incomplete, the history alone was helpful, as may be seen in Table V.

With the exception of gonorrhea, the part that these diseases played in the production of sterility due to injury to the reproductive mechanism is difficult to evaluate. It is interesting to note that of the patients who became pregnant, one gave a definite history of gonorrhea, 13 had had mumps.

TABLE V. HISTORY OF PREVIOUS SIGNIFICANT DISEASES

DISEASE	NO. OF CASES
Mumps	45
Gonorrhea, definite	5
Scarlet fever	7
Phlebitis	2
Pneumonia	11
Rheumatic fever	1
Tuberculosis	1
Streptococcic infections not classified	2
Typhoid	1
Typhus	1

TABLE VI. HISTORY OF PREVIOUS SIGNIFICANT SURGERY

OPERATION	NO. OF CASES	NO. OF WOMEN PREGNANT
Appendectomy		
Ruptured	4	0
Unruptured	54	
Suspension of the uterus	9	
Ovarian surgery (removal or resection)	19	4
Salpingectomy	5	1
Ectopic pregnancy	3	
Thyroidectomy	2	
Nephrectomy	1	
Dilatation and curettage	11	
Amputation cervix	2	
Cauterization of cervix	4	
Vaginal plastic	1	
Bartholin cyst	1	
Stem pessary	14	0
Smith-Hodge pessary	2	

A relatively high incidence of surgical manipulations of one kind or another was elicited from the history. This was particularly noteworthy in the patients with long-standing sterility.

None of the cases with a history of ruptured appendix became pregnant under our treatment. Two cases with a history of resection of the ovary became pregnant. Two cases with unilateral oophorectomy for endometriosis became pregnant. One case with a history of salpingo-oophorectomy for a ruptured ectopic pregnancy became pregnant. Two cases with bilateral salpingectomy were included in this series principally because they had presented themselves for study and received tubal insufflation more as an assurance as to their sterility than as a hopeful gesture. None of the fourteen cases with a history of having worn a stem pessary became pregnant or had a history of a pregnancy. In one case, the pessary was so imbedded and overgrown within the cervical canal that surgery was necessary for its removal.

It is logical to suppose that the normally alkaline semen would find in the normally alkaline cervix an environment favorable to spermatic mobility and viability. Conversely, hostile chemical factors should exist where an abnormal cervical pH is present. Vaginal secretions were tested in 103 cases and were found acid in all cases. The pH of the cervical canal was tested in 101 cases; in 52 cases it was on the alkaline side and in 49 cases it was on the acid side.

What changes in cervical and vaginal chemistry occur in association with sexual stimulation and organism in the female cannot be measured. Theoretically, however, cervical secretions should have been unfavorable in the 49 cases. In respect to this factor, no appreciable difference was apparent in the cases becoming pregnant as compared with those not achieving pregnancy. Infections of the cervix and erosions of the cervix are in somewhat the same category. Both chemical and mechanical factors are unquestionably introduced by these abnormalities; the mechanical factors being seen in connection with the Huhner test where the enmeshed and entrapped sperm are so often seen struggling in the tenacious, mucopurulent exudate from an infected cervix. In 66 cases, an erosion of the cervix of sufficient extent to warrant recording was present. In 46 additional cases a deep-seated cervicitis was present, of which three cases had impassable strictures; in 11 more cases, laceration and infection were present. In all, 123 of these cases (59 per cent) presented outstanding cervical pathology, a most impressive figure. Vaginal pathology, such as *Trichomonas vaginalis,* fungus type of vaginitis, etc., were noted in nine cases.

TABLE VII. MECHANICAL-CHEMICAL FACTORS

TYPE	NO. OF CASES
pH vagina acid	103
pH cervix acid	49
pH cervix alkaline	52
Erosion of cervix	66
Infection of cervix	46
Laceration of cervix	11
Infection of vagina	9

TABLE VIII. UTERINE POSITION AS A MECHANICAL FACTOR

Retroflexed uterus in series	20%
Retroflexed uterus in pregnant cases	11%

The retroflexed uterus presents a mechanical factor principally in regard to the position of the cervix which is frequently observed to be out of the seminal pool. Forty-two cases (20 per cent of the series) were observed to have this abnormality. Since this is approximately the incidence among all women, the figure is not impressive. However, a somewhat different evaluation is obtained when it is noted that in the cases in whom pregnancy eventually occurred, only 11 per cent had a retroflexion of the uterus. In other words, it was only half as frequent in these women as in the general female population and in the rest of this series. Faulty position of ovaries and tubes occasionally described as "prolapsed into the cul-de-sac" and very frequently associated with abnormal position of the uterus, cannot be evaluated. But the palpable tube is an abnormal one. The tubes were described as palpable in five cases of which one had a frank tuboovarian abscess. Occult obstruction of the tube is demonstrable only by tubal insufflation.

We are in complete agreement with Meaker and Siegler, who point out that the study of sterility is not properly the investigation of individuals, but rather the study of infertile matings. However, in practice, the gynecologist will have

little or no direct contact with the male half of the problem, depending upon the urologist to balance the study. This may or may not be a fortunate combination but, in any event, since 30 to 40 per cent of sterility factors have been variously estimated to reside in the male, it is an important one. Our own series frankly considers the male indirectly: from his history as obtained from the wife, from the Huhner sperm test, and from condom-bottle sperm tests. The man is referred to the urologist for further studies on the basis of these contacts only. Here the Huhner sperm test was recorded 104 times, and was considered normal in 48 cases, abnormal in 56 cases. The condom-bottle sperm test was recorded 123 times and was considered normal as to count, motility, and morphology in 62 cases; abnormal in 61 cases. By this indirect approach, abnormalities in the male so far as observation of the sperm is concerned, would seem to exist in 50 per cent of the cases. A better appreciation of the role of the male in infertile matings is seen indirectly in the fact that 65 per cent of the husbands of the women who became pregnant had normal sperm, whereas only 44 per cent of the husbands of women failing to become pregnant had normal sperm.

TABLE IX. MALE FACTORS BY INDIRECT OBSERVATION

TEST	NO. OF CASES
Huhner	
normal	48
abnormal	56
Sperm	
normal	62
abnormal	61
Sperm in successful pregnancies	
normal	65%
Sperm in unsuccessful pregnancies	
normal	44%

The principle of tubal insufflation as devised by Rubin is an indispensable procedure in the study of infertility in the female. It is sometimes forgotten, however, that the apparatus demonstrates the presence or absence of patency throughout the entire reproductive tract, although Rubin has shown rather conclusively that the lesser fluctuations on a kimographic tracing are due to tubal peristalsis. In the 210 cases reviewed here, the "Rubin Test" was performed 306 times on 193 women. In the women who became pregnant, patency was demonstrated or achieved at the first trial in 67 per cent; in those who did not become pregnant, in 68 per cent. It was necessary to perform the test twice in 62 cases; in the pregnant women, patency was then demonstrated in 76 per cent of the cases, and in the nonpregnant in 71 per cent. These figures would seem to indicate about an equal incidence of the tubal factor in both groups of women. As shown in the following table, the test was repeated a varying number of times in a decreasing number of patients. Eventually, two patients received the test seven times each, one of these patients eventually became pregnant. In 35 cases occlusion was the final notation, although in many of them the test was performed only one time. Lipiodol studies were performed 17 times, and in the subsequently pregnant group demonstrated patency in four out of five cases. In one case the lipiodol was occluded, as were three Rubins, but pregnancy oc-

TABLE X. TUBAL INSUFFLATION AND LIPIODOL IN MECHANICAL OCCLUSION

TESTS	NO. OF CASES
Total Rubin tests	193
Total Rubin tests done	306 times
Total lipiodol tests	17
Patency first time, pregnant group	67%
Patency first time, nonpregnant group	68%
Rubin test twice	62
Rubin test 3 times	31
Rubin test 4 times	11
Rubin test 5 times	4
Rubin test 6 times	3
Rubin test 7 times	2
Finally occluded	35
Lipiodol occluded pregnant group	1
Lipiodol patent pregnant group	4
Total lipiodol pregnant group	5

curred anyway, clearly demonstrating the sometimes remote value of tubal insufflations and lipiodol injections. The lipiodol was occluded in 6 of 12 cases in the nonpregnant group.

Endocrine Factors

Endocrine factors in infertility are demonstrated in an office study on the basis of: (1) history, (2) physical findings, (3) basal metabolic rate, (4) endometrial biopsy.

Nineteen cases complained of delayed onset of menstruation, the age 16 years or over being taken as a criterion; 29 cases described menstrual irregularities. Hirsutism of the masculine type, infantilism of the primary or secondary organs of reproduction, pelvic girdle fat distribution, prepubertal and pubertal obesity, rapid weight gain, and acne were observed in 26 cases. Fifty-five patients were overweight for height and body structure, 18 patients were underweight. In all, 61 per cent of the cases showed endocrine stigmas of which the majority were ordinary obesity. This would seem to indicate the group so favorably treated by thyroid. At any rate, the fat woman is definitely more often sterile than the thin or normal woman.

Fibromyomas may be endocrine in origin and in effect, or may be mechanical in effect. Probably they are both. These tumors were encountered in 11 cases, of which only one patient eventually became pregnant. The small, cystic ovary is difficult to diagnose by palpation alone. However, the condition was recorded in 17 cases; 29 per cent of the cases with cystic ovaries occurred in the group becoming pregnant. Frank ovarian cysts were found in 12 cases, two of which were subsequently shown to be endometrioma, one of these latter occurring in a patient subsequently pregnant.

The basal metabolic rate was determined in 125 cases. It was normal (minus 10 to plus 10) in 74 cases. Subclinical hypothyroidism (0 to minus 10) was not considered. It was below normal in 46 cases, although had the subclinical group been included here, the figure would be much higher. It was above normal in five cases. Thirty-six per cent of the cases upon whom the basal metabolism rate was done were, therefore, clinically hypothyroids. Again the

TABLE XI. MISCELLANEOUS ENDOCRINE FACTORS

TYPE	NO. OF CASES
Delayed onset	19
Irregularities	29
Stigmas	26
Obesity	55
Underweight	18
Total endocrine stigmas	61%
Fibromyomas	11
Pregnant	1
Cystic Ovaries	17
Pregnant	29%
Ovarian cysts	12
Endometrioma	2
Pregnant	1

TABLE XII. THE THYROID AS AN ENDOCRINE FACTOR

Total number of cases tested	125
Number of cases, basal metabolism rate normal	74
Number of cases, basal metabolism rate below normal	46 (36%)
Number of cases, basal metabolism rate above normal	5
Hypothyroids pregnant	30%

TABLE XIII. THE OVARIES AS AN ENDOCRINE FACTOR

TYPE	NO. OF CASES
Total biopsies	135
Ovulation positive	87
Endometrial hyperplasia	24
Endometrial hypoplasia	11
Endometrial infection	13
No ovulation but pregnancy	9

reason for the efficacy of thyroid in treatment is emphasized. Less than one-third of the cases of hypothyroidism became pregnant.

It is axiomatic that ovulation must occur if conception is to occur. We are fortunate in having ready access to the endometrium in which this event is reflected. We are in accord with the statement that an endometrial biopsy showing a failure to ovulate means only that the woman failed to ovulate during that particular cycle. Similarly, the typical secretory endometrium indicative of ovulation does not mean that the woman always ovulates. However, it cannot be denied that we will be right many more times than not if we assume that she ovulates regularly if the endometrium is secretory. Biopsies of the endometrium were obtained by the use of the aspiration curette in 135 cases. Ovulation was diagnosed in 87 of these, endometrial hyperplasia in 24 cases, endometrial hypoplasia in 11 cases, and infection in 13 cases. The conclusion that a single biopsy does not indicate ovulation during every cycle is confirmed by the fact that nine cases eventually becoming pregnant showed no evidence of ovulation. Our treatment with the gonadotropes was so infrequent and so poorly evaluated that we do not ascribe this occurrence to the effect of our therapy.

Method of Treatment

In an attempt to overcome the various types of mechanical factors encountered in the infertility of this series, the following surgical procedures

were employed: cauterization of the cervix, 27 patients (13 of whom became pregnant); Hyams conization of the cervix, 7 patients (2 of whom became pregnant); modified Sturmdorf amputation of the cervix, 16 patients (6 of whom became pregnant); suspension of the uterus, 2 patients (none became pregnant); dilatation and curettage, 2 patients (one of which became pregnant); oophorectomy, 4 patients, of which 2 were for endometrioma, one for solid tumor of the ovary (one of whom diagnosed endometrioma became pregnant); dilatation of the cervix, 7 patients (3 of whom became pregnant). Plastic surgery to overcome stricturing of the introitus was performed one time, and this patient became pregnant. The production of an endometrial groove before expected ovulation in the manner described by Rock was done once, and the patient became pregnant immediately following. Other methods utilized in overcoming mechanical factors were: Smith-Hodge pessary, 12 patients (6 of whom became pregnant); knee-chest, 10 patients (5 pregnant); artificial insemination, 1 patient (no pregnancy). It must not be inferred from the above that we credit the procedure indicated for the pregnancies that occurred in this group. In all of these patients, other methods of treatment were also employed.

TABLE XIII. TREATMENT OF MECHANICAL FACTORS

PROCEDURE	NO. OF CASES	NO. PREGNANT
Cauterization of cervix	27	13
Hyams	7	2
Sturmdorf	16	6
Suspension	2	0
Curettage	2	1
Oophorectomy	4	
endometrioma	2	1
solid tumor	1	0
salpingo-oophoritis	1	0
Dilatation cervix	7	3
Vaginal plastic	1	1
Rock procedure	1	1
Smith-Hodge pessary	12	6
Knee-chest	10	5
Artificial insemination	1	0

TABLE XIV. TUBAL INSUFFLATION AS THERAPY

Times performed	113

Tubal insufflation is both diagnostic and therapeutic; it is not possible to tell when it is the one and when it is the other. We have rather arbitrarily said that it should be considered as a treatment if used more than one time. This seems justified since the second, third, fourth, etc. Rubin tests were performed because the first showed excessively high pressures to establish patency or met with frank occlusion. On this basis, the procedure was used as treatment 113 times. There was one case in which the heavy oil, lipiodol, seems to have produced patency, although the x-ray did not show this and the Rubin test had been done three times previously.

With the exception of thyroid, none of the endocrines received a fair trial in our hands. Sixty-one cases received thyroid extract; 36 per cent of the cases

who received thyroid became pregnant and, of all the cases who became pregnant, 30 per cent received thyroid. We are convinced that this drug is an excellent one in the treatment of infertility. The estrogens, progesterones, and gonadotropes were used in 22 cases. Their use was essentially empirical and the results obtained, if any, cannot be evaluated. Vitamin E was used in 18 cases. We have no opinion regarding its efficacy.

TABLE XV. THE ENDOCRINES IN THERAPY

	NO. OF CASES	PREGNANT
Thyroid extract	61	36%
Steroids and gonadotropes	22	
Vitamin E	18	

Result of Treatment

We have a record of 73 pregnancies in this series of 210 cases (35 per cent). This total includes 53 normal, living babies (25 per cent). Nine pregnancies ended in abortions or miscarriages. One ended in a tubal pregnancy. Ten were recorded as pregnant with the outcome not indicated; seven of these are pregnant at this time so that the outcome must be awaited. At the time this paper is completed, our follow-up data has not been completed. It has been noted, however, that additional reports indicate about one successful pregnancy in each four cases, and we, therefore, do not anticipate that subsequent data will modify our statistics to any appreciable extent.

TABLE XVI. RESULT OF TREATMENT

	CASES	PER CENT
Pregnancies	73	35
Living babies	53	25
Abortions and miscarriages	9	
Ectopic	1	
No record of outcome	3	
Now pregnant	7	

Summary and Conclusion

We can now answer the question asked in the first part of this paper. One of each four women who complain of infertility will succeed in producing a normal, viable offspring under treatment as we employ it.

The longer the woman accepts her infertility without treatment, the less success will be had with any efforts to correct it.

Cervical erosion, infection, and general pathology were a surprisingly frequent finding in this group.

Abnormalities of the sperm occurred in 50 per cent of the male partners.

Tubal insufflation is of outstanding value both diagnostically and therapeutically.

Endometrial biopsy is diagnostically essential, but, with the exception of thyroid, the endocrines were poorly evaluated.

Thyroid is a valuable drug in the treatment of infertility.

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COEXISTING CANCER OF THE OVARY AND FUNDUS*

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THE purpose of this paper is to record a case of cancer of the ovary and fundus coexisting and to consider available relative information.

This patient was seen first May 5, 1939. She was 47 years old and had been married twenty-four years, with one child, aged 23 years. Her chief complaint was irregular bleeding for the past two years. This irregularity was described as prolonged periods, practically continuous bleeding. Her menstrual history had been normal until two years ago. There had been no operations, but labor was difficult, requiring forceps. The patient stated that she was never well after labor. Examination showed extensive cystic degeneration of the cervix with large erosions. The pelvis was filled with a large irregular mass which extended nearly to the navel. The provisional diagnosis was extensive cervicitis and multiple fibroids of the uterus. The cervical and endometrial biopsy was done on May 9, 1939. After passing sound into the cervix, a considerable amount of material was expelled, which was apparently carcinoma, and microscopic study showed it to be adenocarcinoma. The biopsy from the cervix showed cervicitis only. This examination was followed by high temperature, chills, and other evidences of infection. After several weeks, when the patient's condition permitted, she was given deep x-ray therapy. After two and one-half months' hospitalization, the patient was discharged and her condition was found to be essentially the same, except slight mobility of the tumor. The bleeding had been controlled, but pain was severe. She was offered surgery at this time, though the prospects seemed most discouraging. An operation was performed on Sept. 21, 1939. At this time, the mass was most prominent in the right pelvis. The mass, which still extended nearly to the navel, was fairly movable, although the motion was limited. A low midline incision was made, and the principal mass was found to be derived from the right ovary. This mass was covered by many loops of intestines, ilium, and sigmoid, which were adherent to the mass by inflammatory adhesions. The uterus was pushed to the left, and was of normal size. The left tube and ovary were adherent to the left pelvic wall and broad ligament by fine inflammatory adhesions. The left ovary was degenerated and atrophic. The liver was palpated, no nodules were found, and there were no palpable retroperitoneal glands. The adhesions about the right ovarian mass were separated with great care, but, in separating the adhesions, the mass was ruptured and was found to contain a large amount of thick yellow pus. This pus was apparently coming from the degenerating ovarian malignancy. After the mass had been completely freed and removed, the left tube and ovary were likewise freed. Bilateral salpingo-oophorectomy and panhysterectomy were done. The cancerous growth was separated from the coils of intestine to which it closely adhered. The postoperative diagnosis was "Carcinoma of the right ovary, pus formation and degeneration of the right ovary, partial intestinal obstruction, inflammatory adhesions, carcinoma of the fundus." The laboratory diagnosis was, "Adenocarcinoma and multilocular cystadenoma of one ovary; adenocarcinoma of the uterus; chronic endocervicitis; chronic salpingitis, bilateral."

*Read before the meeting of the South Atlantic Association of Obstetricians and Gynecologists, Feb. 16, 1946.

Comment

It is noted that this patient's symptoms of irregular bleeding continued over a period of two years before any advice was sought by the patient. This is surprising, as the patient's mother died of cancer. This patient is well after six years and shows no evidence of cancer in her pelvis or anywhere else. It is remarkable that a cancer so advanced should have even a six-year cure by any means whatever. There was nothing unusual about the treatment, which was x-ray followed by panhysterectomy and bilateral oophorectomy and salpingectomy. The tumor was obviously partially radiosensitive, and this effect, no doubt, rendered the operation and the cure possible. Ewing suggested that spontaneous regression of these tumors occasionally occurs. Meigs attributes the regression of papillary peritoneal implants following bilateral oophorectomy to the removal of some of the source of estrogen production. The favorable effects on carcinoma of the prostate following removal of the testes has been observed by some. It is possible that all of these influences may have been helpful and aided in the recovery of this patient. We know that there will not be many cases which will recover under the circumstances, but there is some encouragement not to leave such cases to die without making any effort to cure them.

This condition, cancer of the ovary and fundus of the uterus separately, seems to be a relatively rare condition. However, Novak[6] found seven such cases in a series of 147 cases of adenocarcinoma of the corpus. The one which I report is the only one found in a series of 69 cases of adenocarcinoma of the fundus treated at the Norfolk General Hospital during a period of ten years. I have recently found reports of four other cases occurring in the literature since 1920. One of these[1] was obviously a Krukenburg tumor which involved both ovaries and the uterus, probably not a very uncommon occurrence in a Krukenburg tumor. It is quite possible that this search is hampered to some extent by nomenclature, as there are probably others which have been classified differently. Of course, in the latter stages of extensive cancer of the pelvis it might often be seen. A very brief abstract of these cases follows:

CASE 1.[2]—Patient was 17 years of age. Bilateral adenocarcinoma of the ovary and of the neck of the fundus; histologic structures identical in all three locations. The author assumes the pathogenetic probability here was that the ovary was the original site, and the cells were picked up by the fimbriated end of the tube and carried to the endometrium. The whole tumor mass here extended above the umbilicus. At operation, both tubes and ovaries and complete hysterectomy were done. The patient was dismissed in good health on the twenty-eighth day. There is no note on the future.

CASE 2.[3]—This patient was 63 years old. The symptoms were the usual—pain, bleeding, and mass. Laparotomy revealed cystic tumor of the right ovary about the size of a fist with peritoneal extension. Subtotal hysterectomy was done. The uterus was opened at the time of operation and showed obvious cancer. Report of microscopic study was "cancer of the ovary and fundus." Patient died twelve days after operation.

CASE 3.[4]—This patient was 50 years of age. Symptoms were bleeding, pain, and a mass in the lower abdomen. Laparotomy revealed a nodular uterus and a large cystic mass on the left side. Hysterectomy and removal of the cyst was done. Study of the tissue showed cancer in the ovary and the uterus. Patient died a few months later from extension of growth.

Alfieri,[5] in his monograph on the pathogenesis, gives four distinct combinations of the pathogenetic possibilities of the two carcinomatous tumors:

1. Both uterine and ovarian carcinoma are primary and independent.

2. The ovarian carcinoma is primary and the uterine secondary.
3. The uterine carcinoma is primary and that of the ovary secondary.
4. Both neoplasias are secondary to one originating outside of the sexual apparatus.

As to whether they originate in the ovary or the uterus more frequently, there is some difference of opinion. Novak expressed the belief that they commonly originate in the uterus and are transmitted through the lymphatics to the ovary. Since cancer is more commonly transmitted through the lymphatics, there is much evidence in the favor of this plan.

Sampson's theory that the regurgitated menstrual blood carries implants of either endometrial tissue or cancer to the ovary or elsewhere is a possible explanation. In my case, the tumor of the ovary was far advanced and extensive, whereas the uterus was of practically normal size, and the endometrium only was involved. Under these circumstances, it would seem reasonable to suppose that the ovary was the original site of the tumor. It would also seem a possibility that the cells were picked up by the fimbria of the tube and carried to the endometrium. Of course, the lymphatics are also a possibility. The fact that the type of cancer cells in both tumors are identical in both ovary and uterus would lead one to believe that they were not of independent origin.

References

1. Schenk, F., and Sitzenfrey, A.: Ztschr. f. Geburtsh. u. Gynäk. **60**: 392-419, 1907.
2. Zacutti, A.: Riv. d'ostet. e ginec. prat. **10**: 635-639, 1928.
3. Dambrin, P., Fabre, J., and Tarrène: Bull. Soc. gynéc. et d'obst. **27**: 790, 1938.
4. Vanverts, J.: Bull. Soc. gynec. et d'obst. **19**: 551, 1930.
5. Alfieri: Folia Gynecologica, v. ii, fasc. 3, 1909.
6. Novak, Emil: Am. J. Obst. & Gynec. **14**: 470, 1927.

PHYSIOLOGY OF LABOR*

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IN THE physiology of labor much importance should be placed upon the muscular action of the uterus and its results in expulsion of a living fetus. As a prelude it may be stated that nature has developed an enormous store of checks and balances, many of which are only surmised and some may be of the utmost complexity. Among the latter are the labor functions of acetylcholine, cholinesterase, epinephrine, posterior pituitary extract, histamine, and sympathetic and parasympathetic nervous control, as well as the various endocrine functions in health and in disease. In addition, the actions of the myriads of possible chemicals upon these complex processes is practically a closed book, but also an inviting field for investigation. These are all subjects for the most productive of research, but they require energetic prosecution by means of obstetricians, biochemists, pathologists, physiologists, and pharmacologists. Two of the most intriguing phases of physiology of labor are the cause of the onset of labor and the train of events that leads to eclampsia. Since the early work of Schatz[1] in 1871 to 1872, intrauterine pressure studies have been made by Hensen,[2] Rucker,[3] Bourne and Burn,[4] Wielock,[5] Salerno,[6] Bickers,[9] and Moir,[10] using balloons placed into the uterine cavity before, during, or after labor.

During the past nine years, Woodbury[7, 11] and associates, working with obstetrical patients in the University Hospital, have obtained numerous prolonged continuous records made with the Hamilton closed fluid differential manometer. By this means simultaneous continuous exact pressure readings are optically recorded of any of the following: (a) intrauterine pressure above the fetal head, or (b) below the fetal head, (c) the stomach pressure, (d) the maternal intra-arterial pressure, (e) intravenous pressure. Besides the simultaneous record of these individual pressures, a record may be made of the differential between any two.

Throughout pregnancy there are the Braxton-Hicks contractions causing minor changes in the pressure intermittently every two minutes or so, enough to maintain some flow of blood in the intervillous placental spaces. These probably serve to oxygenate the uterus and the fetal blood. At the onset of labor these contraction waves acquire greater amplitude, and the intrauterine pressure rises from a tone pressure of 5 mm. Hg to several times that amount, so that there occurs a sensation of labor pain. This pain sensation arises at various pressures from 25 to 35 mm. Hg, depending upon the irritability of the patient. During normal labor then, in the first stage, the intrauterine pressure rises slowly with each contraction to a peak of 35 to 60 mm. Hg, and then equally slowly falls to the uterine tone pressure of 5 to 8 mm. Hg. The length of the palpable contraction during which the uterus is felt to be firmly

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contracted is approximately forty seconds and of the interval between contractions, two to five or more minutes. In the second stage after full dilatation of the cervix, the apex of the contraction wave usually is higher than in the first stage, and may rise to a maximum of 110 mm. Hg and the "intercontraction" tone remains higher at 10 to 12 mm. Hg, about twice what it was in the first stage. During the second stage the more or less voluntary contraction of the abdominal muscles practically doubles the effective intrauterine pressure so that the combined pressures caused by the contraction of the uterine muscle and of the abdominal muscles may reach 260 mm. Hg (which was the highest recorded). The effective pressure in expelling the fetus whose average presenting head diameter was 9 cm., calculated from the uterine contractions, was between 8 and 18 pounds. The abdominal muscles increased the expulsive forces to 22 to 46 pounds. These were all in well-developed sturdy primiparas.

Further use of the differential manometer revealed that the pressure within the placenta is such that the maternal blood is being squeezed out during the uterine contraction, usually into the vena cava, but in one case, actually into the aorta also, for the intrauterine pressure was higher than the maternal arterial pressure. The effect is naturally greater if the maternal blood pressure is low. This action causes approximately a pint of blood to be thrown back upon the maternal systemic circulation at each labor contraction, raising the venous pressure approximately 10 mm. Hg, and may be a factor in the danger of labor in decompensating cardiac patients. There is a slight increase in arterial pressure during a labor contraction, greatly augmented if there is coincident "bearing down" by abdominal muscular action.

Physiologic Effect Upon the Fetus.—During the first stage of labor, the pressure changes equally affect both the entire fetus, as well as its placental circulation, therefore it is practically without damage unless something obstructs the oxygen and the metabolites' supply to the fetal blood. However, during normal labor there is probably a better exchange of oxygen and metabolites from the maternal blood than previously, because of the increased maternal blood flow due to the heartlike action of the uterus with its contraction as systole and its prolonged interval with low muscular tone as diastole. In the second stage only is there greater pressure above the fetal head than below, but this again is intermittent and allows for adequate oxygenation of the fetal blood.

Abnormal Labor.—During the years of study there were not infrequently patients found who had abnormal physiology of labor. These, as a rule, were the so-called dystocia dystrophy type well described by DeLee, Horner, and others. It was also found that similar physiologic alterations of normal labor occurred in practically all parturients who had abnormal labor, especially in those who had inadequate therapy during labor or in prolonged obstructed labor. Some of the factors influencing the production of this altered labor were found, and, coincidentally, some measures of prevention or correction even after several days of labor were ascertained.

In dystocia-dystrophia syndrome, the patient often has the characteristics of pituitary dysfunction of increased weight, short stature, or stocky build, with relatively long torso and short thighs. Her fingers are short and stubby. She may conceive with difficulty, and when pregnant, if she doesn't abort, often has a tendency to go "over term" and then enter a prolonged and tedious labor. Besides, she more often is subject to abnormal weight increases with attendant inclination to toxemias of pregnancy. In these the abnormality of labor is generally not due to alterations in the pelvic structures as has been thought to be the case. A study of the pelvis by exact roentgen-ray measurements in eight cases revealed that seven were gynecoid in type with moderate contraction of the anteroposterior diameter below 10 cm. in two, slight contraction (10 to 11 cm.) in three, large gynecoid pelvis in one. The eighth, a Negro woman, had a contracted android type of pelvis. Since these observations were made, many other cases have been encountered, and in not one was there found coincident fetopelvic disproportion enough to preclude vaginal delivery. The abnormality of labor then is due mainly to altered physiology of the uterine contractions. Moreover, this same altered physiology has been found to be present in almost all other cases of prolonged labor, and its onset is earlier if the labor is poorly managed. The characteristics of these abnormal labor states appear in the continuous record of the intrauterine pressures. First, the labor contraction waves are shorter, more peaked, and of variable amplitude as well as variable intervals of recurrence; second, and of such importance as to be almost pathognomonic, the intercontraction tone remains much above the normal of 5 to 8 mm. in the first stage of normal labor, and of 10 to 12 mm. in the second stage. In the dystocia dystrophy type of labor this tone may rise to 15 to 18 mm. Hg or more. This, if long continued, causes disastrous results, not only to the fetus, which becomes hypoxic, but also to the mother, wearing her out by fruitless nagging pain which, because of the lack of blood and oxygen to the uterine wall, fails in enough force to dilate the cervix and expel the fetus.

All experienced obstetricians have repeatedly seen just such cases, although they may not have recognized the crucial fact that the uterus remained unusually firm between "pains" to such an extent that in some instances the patient's sensation of pain was continuous. Since the high intercontraction tone seemed to be the most characteristic finding in these cases, much interest was taken to ascertain the effect of various anesthetic drugs upon them. Only one was found which had the ability to abolish in most cases the abnormal contractions with the intervening elevated intrauterine pressure. This was morphine. The other anesthetics and barbiturates may be of value in preventing the occurrence of this condition, but are of little or no influence in curbing the condition once it begins. The effects of the anesthetics upon normal labor contractions are revealed in tracings. It was also found that, while morphine in adequate dosage, usually at least ¼ grain subcutaneously, was effective in abolishing abnormal labor contractions and of relieving the uterine tension between contractions, that it had no effect upon normal labor contractions after they have been definitely established. In addition, it frequently changed

abnormal labor into normal labor in which the cervix, heretofore stationary in dilation, soon began to dilate, and within in a few hours (often surprisingly few) the fetus delivered spontaneously. Besides, all other anesthetics and hypnotics, as usually used, were found to have little adverse effect upon the normally acting uterus. There was a small percentage of cases in which morphine administration was not followed by prompt relaxation of the uterus, and in one instance in which the uterine tone between contractions was estimated by palpation to be at least 35 mm., ¼ grain morphine subcutaneously had no appreciable effect in relaxing the uterus, and the fetus continued to be in poor condition (pulse rate of 70), and in the course of one hour the heart rate gradually became slower and ceased entirely. This was not a condition of a contraction ring, because the uterus continued to have intermittent contractions and spontaneously expelled the dead fetus twelve hours later, in spite of abnormally high tone between contractions. It may be that a larger dose of morphine or deep anesthesia by another agent would have been effective. Or this may have been of different origin than usual, and possibly epinephrine, magnesium, or some other drug may be found to be more effective than morphine in a few instances.

Other Causes of Dystocia Dystrophy Syndrome Type of Labor.—Besides the constitutional type of patient subject to dystocia dystrophy syndrome, it has been discovered that any patient in labor may be thrown into similar abnormal type of labor by repeated administration of oxytocic drugs, pituitrin, and ergot preparations. The intercontraction tone gradually rises with repeated doses of the drugs until complete tetany exists.

It was found that in certain cases of toxemia with hypertension, large weight gain, edema, often associated with dehydration and anemia, there may be development of this abnormal type of labor. In several instances it was found in otherwise normal and well-nourished women with adequate pelvic canals who were markedly anemic. It also developed in several women with moderate to severe grades of fetopelvic disproportion, as determined by exact x-ray studies. These, as a rule, were those whose labor management was not ideal according to standards elsewhere outlined.

References

1. Schatz, F.: Arch. f. Gynäk. 3: 58, 1871-72.
2. Hensen, H.: Arch. f. Gynäk. 55: 129, 1898.
3. Rucker, P.: J. Lab. & Clin. Med. 10: 390, 1925.
4. Bourne, A. W., & Burn, J. H.: Lancet 2: 694, 1928.
5. Wielock, J.: Zentralbl. f. Gynäk. 51: 129, 1927.
6. Salerno, J. P.: Am. J. Obst. & Gynec. 36: 294, 1938.
7. Woodbury, R. A., Hamilton, W. F., and Torpin, R.: Am. J. Physiol. 121: 640, 1938.
8. Reynolds, S. R. M.: Physiology of the Uterus, New York, 1939, Paul B. Hoeber, Inc.
9. Bickers, W.: Am. J. Obst. & Gynec. 43: 815, 1942.
10. Moir, J. C.: J. Obst. & Gynaec. Brit. Emp. 51: 181, 1944.
11. Woodbury, R. A., and Abreu, B. E.: Am. J. Obst. & Gynec. 48: 706, 1944.

THE USE OF PENICILLIN IN REPAIR OF COMPLETE PERINEAL LACERATIONS*

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I WISH to report four cases of complete perineal laceration, operated upon since June, 1945, in which penicillin was given after the operation as a routine procedure. They all had the same preoperative preparation, and the same type of operation was used. The preoperative preparation included a general physical examination, and special attention was given to correcting any existing anemia or cervical erosion. One week before the operation, 60 grains of sulfasuxidine were given daily. A sulfathiazole suppository was inserted in the vagina at bedtime, and a douche of one-half cup of vinegar to a quart of water was used the next morning. Two days before the patients were admitted to the hospital, a mild laxative was given, and they were also put on a non-residue diet. The patients were admitted in the evening, and the operations were performed the following morning.

In all these cases, there was an absence of a part of the anterior rectal wall. In one case there was very little perineal tissue on the right side of the vagina. Tincture of merthiolate was used to prepare the operative field. A transverse incision was made on the posterior vaginal wall, going high enough up in the vagina to make a flap to be used as the anterior rectal wall. This transverse incision across the vagina was curved to the vaginal outlet, and dissected very carefully so as not to buttonhole it, and also to leave enough tissue on the flap to give it an adequate blood supply. The dissection of this flap was stopped just at the junction of the rectal and vaginal mucosa. The vaginal mucosa was dissected forward to give a flap to be used in the perineorrhaphy. The sphincter muscle was then isolated and brought together across the outer flap of the posterior vaginal wall and sutured with number one chromic catgut. It was then reinforced by suturing the adjoining fascia over this flap. Care was taken that there was no tension in bringing the muscles together. The next step was to suture the vaginal flap to the skin edge and follow with the usual perineorrhaphy.

Postoperatively, the patient was given a nonresidue diet for four days, and 10,000 units of penicillin in the muscle every three hours. On the fourth post-operative day, one-half ounce of mineral oil was given three times a day, and on the next day 2 ounces of mineral oil were injected in the rectum through a catheter. If there were no results from the preceding treatment, the patient was given a mild laxative that night.

Case Reports

CASE 1.—Mrs. W. T. D., aged 28 years, was operated upon on June 25, 1945. She had had one pregnancy four years ago. Labor had been difficult and forceps were used. She was left with a complete laceration, and part of the right perineal body was gone. In this case, I dissected where the sphincter was supposed to be, and obtained what I hoped was the sphincter, but was not sure of it. I had to pull the left side of the perineum over and sew it to the fascia of the pubic bone. This case was so bad, and since penicillin was being used for everything else, I decided to try it on her. She was in the hospital for fourteen days,

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and spiked a temperature to 100° F. for ten days, with the highest temperature being 100.4° F. for one day. On the ninth postoperative day, after her bowels had been moving through the rectum, some feces were found in the vagina. On pelvic examination, the perineum was found to be intact and in good repair. Rectally, there was a defect where the vaginal flap had been sewed to the skin. Potassium permanganate douches were given. After they had been used for two days, the solution returned clear, and no feces have been found in the vagina since. When the patient had her first pelvic check-up, a granulating area was found on the anterior rectal wall near the skin edge. This was painted several times with silver nitrate. She now has a good perineal body, has good control of her bowels, but at times poor control of gas. The latter is gradually improving.

CASE 2.—Mrs. D. W., aged 61 years, who was operated upon on Oct. 8, 1945, had had four children, the youngest 20 years old. She had a complete perineal laceration with her last child. She had a fungus infection around the rectum. She was in the hospital for fourteen days following the operation. Her temperature ran around 100° F. for six days, with one day a maximum of 100.4° F. She passed a small amount of blood on the tenth day. A pelvic and rectal examination showed a good perineum. She has good control now of both bowels and gas.

CASE 3.—Mrs. B. M., aged 41 years, who has four children, was operated upon Nov. 2, 1945. She had had no bowel control for fourteen years. This patient, in addition to the perineal repair, had a suspension, ligation of tubes, and an appendectomy. She was in the hospital for ten days and had temperature over 99° F. for three days, the highest being 100.2° F. for one day. She now has good control of her bowels and gas, and has a good perineum.

CASE 4.—Mrs. A. W., aged 45 years, who has 10 children, was operated upon Nov. 26, 1945. She had had no control of her bowels since the first baby was born twenty-four years ago. She was told that if she was repaired, she could have no more children. She was in the hospital ten days. Her highest temperature was 99.2° F. on one day. She now has a good perineum and good control of both bowels and gas.

Summary

The four patients cited stayed in the hospital an average of twelve days. The highest temperature charted was 100.4° F. One patient had a fair result, three had excellent results. The postoperative use of penicillin in complete perineal repair seemed a definite advantage.

LATE POSTPARTUM HEMORRHAGE*

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AS DEFINED in this paper, late postpartum hemorrhage indicates prolonged or excessive uterine bleeding beginning after the first day following delivery. The attempts of other authors (Roberton and Kleinwachter[1]) to extend the interval to reach from the first to the twenty-eighth day postpartum, and to subgroup an early and later type, offer no advantages. The frequency of l.p.p.h.† is difficult to ascertain because of the paucity of reports. Williams[13] and DeLee[14] make only brief mention of the subject, while Davis and Schuman omit any reference to its occurrence. In American literature only one report by N. H. Williams appeared on this subject since 1939.[12] Chiare and Roberton[1] record an incidence of 1:250 to 1:300 for the late group of postpartum hemorrhage from all causes. This paper, however, excludes cases of l.p.p.h. from ruptured varicies or atheromatous vessels, from coincidental tumors (fibroids or carcinoma), from lacerations (cervical, perineal, and vulval), and from uterine inversion.

It deals with late postpartum bleeding due to: (1) Retained placental fragments. Focal placental accreta is not recorded in this group, but there is one case of a retained succenturiate lobe. The remaining cases are fragments derived from normal placentas. (2) Uterine abnormalities in involution of the placental site. (3) Uterine abnormalities in retention and separation of the decidua vera.

Retained Placental Fragments

Stadfeldt (quoted by Siegel[9]) found seven cases of retained placental fragments in 70 autopsies performed upon postpartum women. The cause of death, however, was not stated. At the Brooklyn Jewish Hospital there were 32 cases of retained placental fragments after 32,155 deliveries, an incidence of 1 to 1,005 cases. There were five additional cases confined in other institutions, making a total of 37 cases of this group encountered between Jan. 1, 1934, and Sept. 1, 1944. While generally agreed that true Credé maneuver or manual removal of the placenta are predisposing causes in retention of placental fragments, the hurried conduct of the third stage of labor can be a paramount factor. It is, therefore, necessary to record our management of the third stage of labor. Delivery is conducted under gas-oxygen-ether anesthesia. At the birth of the child, ½ c.c. of pituitrin is administered intramuscularly, and anesthesia is lightened. With rise in the height of the fundus, or descent of the cord, a modified Credé is performed, and the spontaneously separated placenta is expressed. One c.c. of ergotrate is then administered intramuscularly, and the uterus is carried well out of the pelvis. The placenta and membranes are then inspected. A course of $\frac{1}{320}$ grain ergotrate tablets every four hours for

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†Late postpartum hemorrhage, elsewhere designated by l.p.p.h.

six doses is routinely administered during the first day post partum. It must be emphasized at this point that detection of a missing fragment smaller than a cotyledon is not easy if the placenta has been compressed or traumatized in its delivery. Remaining in situ a retained fragment undergoes one of the following courses: (a) spontaneous expulsion (4 cases); (b) operative removal after one or more episodes of bleeding (31 cases); and (c) enmeshment or polyp formation (2 cases).

A. *Spontaneous Expulsion of a Retained Placental Fragment.*—It may be complete or partial, and four such cases have been encountered. Reduction in the size of the uterus during its involution causes separation of the attached fragment. Underlying sinusoids and veins are opened, and intrauterine bleeding follows. Muscle contractions which may ensue help further to separate the retained fragment and favor its expulsion from the uterine cavity. The clinical manifestations of this group are abstracted below.

CASE 1.—(AA24,273), gravida ii, para i. The first pregnancy terminated in early complete spontaneous abortion. The current pregnancy continued to term. Labor was without incident, and the third stage was uneventful. The first episode of slight bleeding occurred on the fourth day after delivery and, in spite of a course of ergotrate, staining continued after discharge on the twelfth postpartum day. On the thirty-fifth postpartum day, active bleeding associated with uterine cramps resulted in the spontaneous expulsion of a placental fragment measuring 4 by 3 by ½ cm. All bleeding then ceased.

CASE 2.—(AA35,632) A primipara at term delivered without incident. The placenta was retained for ninety minutes without bleeding. A true Credé maneuver was then performed under anesthesia, and the placenta was delivered, apparently intact. A febrile postpartum course was attributed to an infected perineum. On the tenth day postpartum, the patient bled and, in spite of absence of cramps, a small fragment of placenta was spontaneously expelled. On the sixteenth postpartum day a second hemorrhage followed. This did not respond to ergotrate, and on the seventeenth postpartum day the continued bleeding necessitated curettage. A small residual placental fragment was obtained. The uterus and vagina were then packed and a transfusion of 500 c.c. was given. The postoperative course was uneventful and all bleeding ceased.

CASE 3.—(AA37,476) A para ii, gravida ii delivered without incident at term. The placenta separated spontaneously in five minutes and was expressed seemingly intact. There was moderate bleeding on the third postpartum day. A course of ergotrate was given, resulting in expulsion of a small fragment 3 by 2 by 1 cm. The low grade temperature of 100.6° F. which had continued from the first postpartum day then returned to normal.

CASE 4.—(AA196,724) A primipara at term delivered without incident. The placenta separated spontaneously after twenty minutes and was expressed, supposedly intact. On the second postpartum day, there was moderate bleeding associated with passage of a placental fragment, 2 by 1 by 1½ cm. There were no cramps. The temperature remained elevated to the fourth postpartum day. Microscopically, the tissue fragment was free from infection.

B. *Retained Placental Fragments With Bleeding, Requiring Surgical Intervention.*—

1. *Afebrile:* Of 24 patients comprising this group, 14 were primiparas and 10 were multiparas. Labor was normal in 12 patients. Eight patients were

TABLE I. RETAINED PLACENTAL FRAGMENTS REQUIRING INTERVENTION

		AFEBRILE	FEBRILE
	Total cases	24	7
	Primiparas	14	4
	Multiparas	10	3
Mode of Delivery	Spontaneous	12	3
	Low forceps	7	0
	Midforceps	1	2
	Breech	1	1
	Version	1 (twins)	0
	Other hospital	2	1
	Home	1	0
Third Stage	Average length	8 min.	19 min.
	Expression	20	5
	Credé	1	0
	Manual removal	0	1

TABLE II. CLINICAL FINDINGS IN RETAINED PLACENTAL FRAGMENTS REQUIRING INTERVENTION

		AFEBRILE	FEBRILE
Onset of Bleeding in Days	1- 5	5	1
	6-10	13	1
	11-15	4	1
	16-20	1	3
	21-25	1	0
	26-30	0	1
Repeated Episodes	0	13	3
	1	2	1
	2	7	1
	3	0	1
	4	2	1
	Lochia foul	0	4
	Abdominal cramps	5	1
Clinical State	No shock	10	2
	Mild shock	4	1
	Severe shock	10	4
Cervix	Patulous	24	6
	Not stated	0	1
Uterine Subinvolution	Mild	4	0
	Moderate	14	4
	Marked	5	2
	Not stated	1	1

delivered by forceps. One breech required manual aid. The second child of a twin pregnancy was delivered by version and extraction. In three cases confined elsewhere the nature of delivery was not known. The third stage was normal in 20 patients, and one required a true Credé maneuver (Table I). The universal symptom of retained placental fragments is abnormal vaginal bleeding. In 18 of 24 cases it appeared within the first ten days following delivery. Most commonly, however, it appeared between the sixth and tenth day post partum (Table II). In the remaining six cases bleeding occurred between the eleventh and twenty-fifth postpartum day. Multiple episodes of varying intensity occurred in most instances. Although the amount of bleeding could not be accurately determined, its extent was in a measure indicated by the systemic condition of the patient. Shock (systolic blood pressure below 100, pulse above 100, pallor, cold skin) in varying degree was present in 14 cases. Of 10 cases in severe shock,

eight reached this status while under conservative medical routine. Abdominal cramps referred to the lower central segment were noted in only five instances. It is our impression that this symptom was associated only with large placental fragments. The lochia was seemingly normal in all patients before the advent of bleeding.

The clinical findings of the uterus cannot adequately be interpreted. Although all uteri were noted as subinvoluted (Table II), accurate mensuration by a calibrated uterine sound, or measurement of the height of the fundus above the symphysis was not employed. It must be noted, however, that distention of the uterine cavity by blood clots would, in a measure, invalidate such findings. Upon examination, the cervix was patulous in all cases. Since this is a normal finding up to the twelfth postpartum day, the value of a patent cervix as a diagnostic aid would apply only to later cases. Thus, in nine cases curetted between the fifteenth and twenty-sixth days postpartum, respectively, a patent internal os was noted in each instance.

TABLE III. THERAPY IN RETAINED PLACENTAL FRAGMENTS

		AFEBRILE	FEBRILE
Medical	Not used	12	2
	Unsuccessful	12	5
Surgical	Curettage	16	4
	Curettage and pack	1	2
	Curage	2	0
	Curage, sponge stick and curettage	5	1
Location of placental fragments	Anterior	4	2
	Posterior	2	1
	Fundus	4	0
	Not stated	14	4
Transfusions	Preoperative	5	2
	Postoperative	5	2
	Pre- and Postoperative	1	1
Pathologic report	Infected	9	3
	Not infected	15	4
Postoperative course	Afebrile	18	2
	Febrile	6	5
	Sulfonamides used	6	2

2. *Febrile:* The febrile group of "retained placental fragment patients" is difficult to define. Elevation in temperature alone does not exclude infection in some other focus (e.g., infected perineum). Exudate of neutrophiles in curetted decidua is a physiologic finding up to the tenth postpartum day. Bacteriologic cultures are difficult to evaluate, for pathogens and nonpathogens can be found in the uterus by aspiration culture after the second postpartum day, even in women free from a morbid course. Blood counts and sedimentation rates, too, are physiologically altered in the puerperium. The presence of neutrophiles within the stroma of the retained villi is sure proof of infection; yet, even in the afebrile group, such fragments were recovered and designated as "infected placental tissue" (Table III). Reversely, too, in the febrile group, only three of seven placentas were reported as infected. It is evident that myometritis could not be detected from curetted material. We

define, therefore, as febrile those cases with an elevated temperature of 100.4° F. or above, occurring after the first postpartum day, and in which any other demonstrable focus of infection is lacking.

There were seven patients in this group, four primiparas and three multiparas (Table I). Three were delivered spontaneously and two by forceps. One breech required manual aid. The nature of delivery was unknown in the patient delivered at another hospital. The average length of the third stage was nineteen minutes in this group, compared to eight minutes in the afebrile group. One patient required manual removal of the placenta after one hour (Table I). The symptomatology was essentially the same as in the afebrile group, and requires no further comment. The onset of the bleeding, however, occurred somewhat later, for only two of the seven cases bled prior to the tenth postpartum day (Table II). In four other cases the initial episode of bleeding occurred after the sixteenth postpartum day. This may be explained by delayed uterine involution due to coincidental infection of the muscle wall. Repeated episodes of bleeding occurred in four of seven cases. The lochia was foul in four of seven cases prior to onset of bleeding. The clinical status of these patients was, as in the preceding group, the best gauge of the severity of blood loss. In this group five of the seven cases exhibited mild to severe shock. The longest preoperative febrile course was nineteen days, with temperature as high as 105° F.; the shortest was five days, with temperature of 103° F. In six of the seven cases wherein the preoperative and operative findings are completely recorded, it was found that the cervices were all patulous and the uteri subinvoluted. The finding of a patulous cervix in infected cases is of some diagnostic import, for onset of bleeding occurs more frequently after the twelfth day postpartum. Tenderness of the uterus upon abdominal or bimanual examination was not noted. Fortunately, the metrorrhagic form of puerperal sepsis as described by Couvelaire was not encountered.

C. *Polyp Formation of the Retained Placental Fragment* (2 Cases).—A retained placental fragment is occasionally transformed into a polyp. It is the result of repeated and incomplete attempts at separation, during which blood is deposited upon the surface of the fragment. Coagulation follows, resulting in the formation of a hemorrhagic mass protruding into the uterine cavity. As a rule, it is of moderate size, and more or less conforms to the size and contour of the cavity. Occasionally it may project through the cervix into the vagina, where it can mask as cancer of the cervix. On gross section, layers of blood and fibrin are adherent to the superior and lateral aspects of the polyp, while its base is separated from the muscle layer by decidua basalis. Microscopically, nutrition of the villi is surprisingly long preserved, but normal forms are intermingled with others in varied stages of necrosis. While the identity of a preserved placental polyp is easily established on palpation of the uterine cavity, those fragmented by curage or curettage often escape detection, especially if intervention follows prior to their hardening and firm attachment to the uterine wall. It may well be that some of the cases reported as retained placental fragments actually belong to this group.

The clinical manifestations of a placental polyp and the physical findings are essentially similar to those of retained placental fragments. Bleeding is more prolonged, or presents recurrent episodes of varied severity. Pain as a rule is lacking. Poor muscle tone may be the cause of prolonged retention of the fragment. To emphasize the clinical characters of placental polypi, the two cases encountered are briefly summarized.

CASE 1.—Mrs. B. G., aged 27 years, a primipara, was delivered normally at term in another hospital, seven months prior to admission. The early postpartum period was normal. About five weeks after confinement the patient supposedly had her first menses. The flow, however, lasted two weeks and was profuse. It soon recurred and continued intermittently for almost six months. Upon admission the uterus was found enlarged, subinvoluted, and soft. Curettage yielded large hemorrhagic fragments of a traumatized placental polyp. The postoperative course was uneventful.

Fig. 1.—The placental polyp is centrally located on the posterior wall of the opened uterus. The external surface is relatively smooth but focally hemorrhagic. The base is attached high in the fundus. The apex of the polypoidal mass projects below the level of transsection.

CASE 2.—Mrs. R. S., aged 27 years, para ii, gravida ii. The first pregnancy and labor were without incident. The current second delivery was uneventful until the thirteenth postpartum day, when profuse vaginal hemorrhage occurred. The uterus, which extended for three fingerbreadths above the symphysis, was packed with plain and iodoform gauze, and intravenous glucose in saline was administered. After removal of the packing on the following day, a second profuse hemorrhage followed. Curettage yielded only moderate amounts of placental tissue. The uterine cavity and vagina were again packed, and a transfusion of 1,000 c.c. of blood was administered. The patient was discharged on the twenty-third postpartum day, only to be readmitted on the same day because of recurrence of profuse hemorrhage. A blood transfusion of 1,000 c.c. was immediately necessary. A fourth recurrent hemorrhage on the twenty-fifth postpartum day led to a supracervical hysterectomy. The postoperative course was normal except for slight wound infection. The patient was discharged on the seventeenth postoperative day (forty-second day postpartum).

The uterus (Fig. 1) measured 15 by 16 by 5 cm. The posterior wall presented a pear-shaped hemorrhagic mass distending the cavity. On microscopic

section through the polypoidal mass, layers of blood and fibrin covered and enmeshed numerous chorionic villi. Centrally, they were more crowded and often viable. At the periphery shadow forms and others in varying phases of necrosis were noted. The underlying layer of decidua compacta was well preserved, and a zone of fibrinoid material separated the placenta from the uterine wall. The underlying veins and arteries were thick and hyalinized. Recanalization of the arteries was present. The veins were hyalinized and filled with thrombi.

Diagnosis

The diagnosis of retained placental fragments is easily established by the history of recurrent episodes of bleeding within the postpartum period. Hemorrhage resulting from separated thrombi at the placental site is rare. Digital exploration reveals multiple polypi which separate with great difficulty. Microscopic examination shows the absence of chorionic villi. A submucous fibroid, traumatized by labor, may produce bleeding during sloughing and detachment of its pedicle. The patulous cervix, however, permits palpation of the uterine cavity, and so the detection of the contained tumor. Inversion of the uterus is easily established by failure to palpate the organ abdominally, while vaginally the protruding fundus is noted through the tight cervical ring.

Therapy

In older literature, medical therapy was strongly endorsed for l.p.p.h., in the hope of attaining spontaneous expulsion of the retained fragment. The risk of infection, and the possibility of operative perforation of the uterus largely dictated this course. DeLee thus advocated temporization until the fifth to sixth week postpartum, then, if intervention were still necessary, removal of the fragment by use of the placental forceps. Williams[13] advised digital palpation of the uterine cavity, localization of the retained fragment, and removal by curage. Siegel[9] advocated curage during the first eight days postpartum, and interdicted against the uterine pack because of the danger of infection. He objected to the use of the curette in the early postpartum period, because of the possibility of uterine perforation, and because of secondary hemorrhage from detachment of thrombi at the placental site. After the twelfth to fourteenth day, he advised curage, followed by the use of the dull broad curette, if the latter were necessary. N. H. Williams,[12] however, deplored "obstetrical treatment" (curage, curettage, and uterine packing), and stated that it is productive of the highest mortality. In the five cases comprising his series of l.p.p.h., it was only beneficial in one case, and useless or harmful in all the others. Williams leans to radical removal of the uterus as treatment of l.p.p.h.

In retrospect, we have followed a middle course. The medical and surgical measures employed are shown in Table III. In general, medical therapy proved unsatisfactory. It consisted in the administration of a course of $\frac{1}{320}$ grain of ergotrate tablets every four hours for six doses, or $\frac{1}{2}$ c.c. of pituitrin every hour for four doses, associated with bed rest. Employed in 12 cases of the afebrile group, it was without result, for the bleeding, though temporarily lessened, soon recurred. It is noted as successful, however, in Case 2 of the

spontaneous group. In the febrile group medical therapy was similarly unsuccessful in five of seven cases in which it was employed. Surgical intervention was, therefore, ultimately necessary in all cases. This included curettage, curage, and use of the placental forceps. In the afebrile group, two were treated by curage and 16 by curettage. An additional patient was packed after curettage, and in five others curettage followed the attempted removal of the fragment by curage and ovum forceps. In the febrile group four patients were treated by curettage, two by curettage and uterine pack, and one by curage, ovum forceps, and curettage. Transfusion was used in 11 of the afebrile group, either pre- or postoperatively or both, using glucose and saline, or plasma intravenously until the arrival of blood. In the febrile group five of seven patients received blood. In the polyp group one was treated by curettage, and the remaining case ultimately required hysterectomy.

Morbidity

In the afebrile group of 24 cases, 18 had a normal postoperative course, while six were febrile (Table III). The longest morbidity was four days. The shortest morbidity of one day was associated with a temperature of 100.6° F. In the preoperative "febrile group" of seven cases, two were afebrile following emptying of the uterus, and five continued with temperature. The morbidity, however, was not severe. Three cases had a morbidity of one, two, and three days, respectively. A fourth case ran a temperature of six days, and the fifth patient a febrile course for seventeen days. This last instance was due to thrombophlebitis. In both febrile and afebrile groups there was no incidence of parametritis, peritonitis, or uterine perforation. The prophylactic use of sulfonamides and penicillin is indicated as a pre- and postoperative measure, and is imperative in the febrile group. Routine employment of uterine cultures at the time of curettage would be helpful in the choice and dosage of these drugs.

Uterine Factors in Late Postpartum Hemorrhage

In the absence of placental fragments, l.p.p.h. is rare. Two uterine factors present as causes: (1) late detachment of thrombi at the placental site with reopening of vascular sinuses and bleeding; and (2) abnormalities in the retention and separation of the decidua vera.

(1) Late detachment of thrombi from the placental site (also designated as "Noninvolution of the Placental Site," by Rutherford and Hertig[8]) was reported by Kustner[7] in 1910. In his two cases liberation of vascular thrombi from the placental site caused profuse bleeding. To understand this factor in l.p.p.h., it may be well to summarize the anatomicophysiological status of the postpartum uterus, as described by Goodall in 1909. In the arteries the fibrous tissue of the media and adventitia undergo hyaline degeneration, and the elastica interna becomes swollen and degenerated. The hyaline of the muscle coat then invades the elastica interna, and enters the vessel lumen replacing the blood clot, so that the lumen is ultimately occluded by hyaline substance, and the artery thus is obliterated. When hyaline thrombosis in the arteries has been partial or absent, the hyaline becomes invested with en-

dothelial cells which form the lining of a new vessel. Next to this new lumen, the hyaline material is invaded by spindle and fusiform cells which later differentiate into muscle cells and fibroblasts, and a new vessel is thus formed within the old, only remnants of the elastica interna and media of the old vessel normally persisting at the periphery (Fig. 2). In postpartum vascular subinvolution, abnormally large amounts of elastic tissue persist about the newly formed artery. In the veins which have no definite elastica interna, all walls contain elastic fibers intermingled with fibrous tissue. In the postpartum period the fibrous tissue swells and becomes hyalinized, thus reducing the lumen of the vein which is filled with clot (Fig. 3). In normal involution, the hyaline in the vein wall is later reconverted into elastic tissue. No detailed description is given of the venous clot. J. Whitridge Williams[10] in 1931 showed that the occluded vessels of the placental site are ultimately undermined by the proliferation of adjoining endometrium, and are lifted from the uterine wall. Protruding as a polypoidal mass, the vessels of the placental site are completely extruded from the organ about the seventh week postpartum.

More recently, Rutherford and Hertig[8] reported three cases of l.p.p.h. due to defective thrombosis in the vessels of the placental site. The first patient, curetted six weeks postpartum, showed only partially obliterated vessels. The second, curetted on the fifteenth day postpartum, showed numerous patent blood vessels at the placental site. Hysterectomy in the third case performed on the twenty-ninth day showed a hemorrhagic polypoidal mass projecting into the uterine cavity. Retained villi were present. Though the arteries were obliterated, many vessels (nature not stated) were incompletely obliterated, for erythrocytes were lying free in their lumina. Two cases of incomplete involution of the placental site were encountered in this study. The clinical features and pathologic reports are as follows:

CASE 1.—(No. 1718) Mrs. X. R., aged 43 years, a gravida viii, para vii, was delivered prematurely of twins at twenty-eight weeks. Manual removal of the placenta was necessary to control active bleeding. The first five days postpartum were febrile, the highest temperature reaching 101.6° F. on the third day. On the ninth day moderate bleeding occurred which was only temporarily controlled by a course of ergotrate, ice bag, and bed rest. Later that day two additional episodes of frank bleeding occurred, and curettage was accordingly performed. The cervix was found patulous, and the fundus was located 3 fingerbreadths above the symphysis. The curettings consisted of a moderate amount of hemorrhagic material. The postoperative course was febrile, the highest temperature reaching 102.4° F. on the fifth postoperative day. There was recurrence of bleeding on that day sufficiently severe to require packing of the uterus and vagina, and the administration of a transfusion of 1,750 c.c. of whole blood. Thereafter, the postoperative course was afebrile, and the patient was discharged on the thirtieth postpartum day when her anemic picture cleared.

The specimen grossly consisted of several irregular hemorrhagic fragments. Placental tissue was not grossly recognizable. Microscopically, the largest fragment was covered with degenerated decidua. The decidual cells had been reduced to hyaline shadow masses. Occasional ones retained their degenerated pyknotic or karyolytic nuclei. There was intensive exudation of lymphocytes and plasma cells which extended into the underlying muscular coat. The superficial muscle fasciculi encircled four contiguous veins (Fig. 4). The endothelial cells were not sharply defined, but occasional swollen and degenerated forms could be distinguished. The muscle and adventitial coats showed swelling and hyalinization. The lumina were filled with feebly formed

Fig. 2.

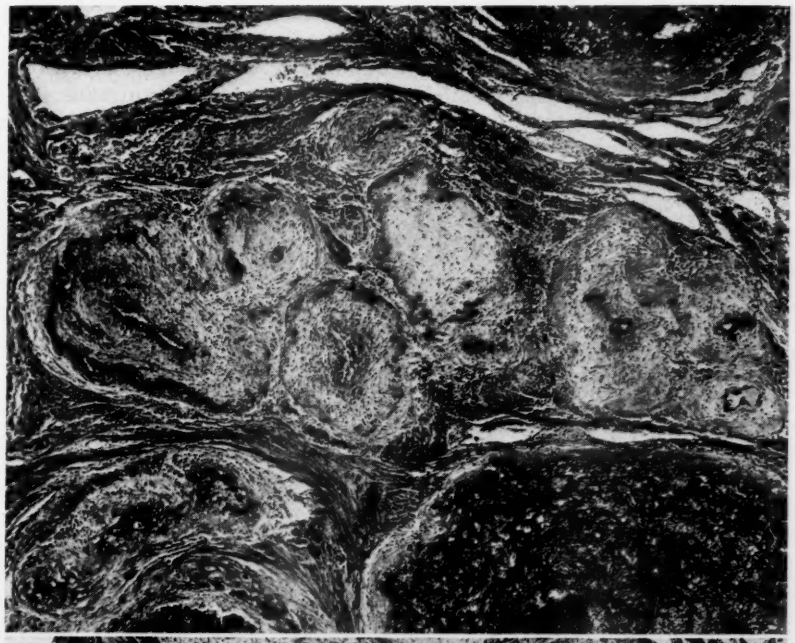

Fig. 3.

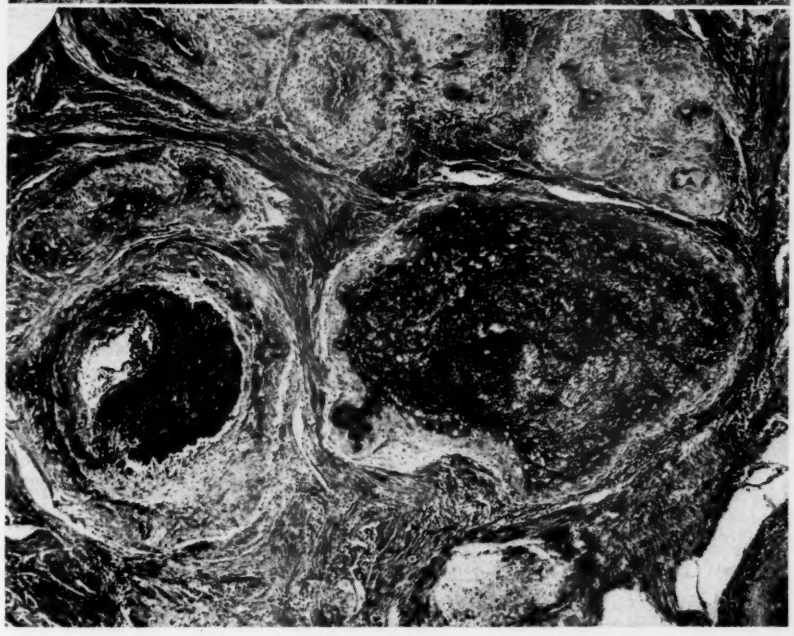

Fig. 2.—(×40) Placental site in a uterus removed by hysterectomy for fibroids ten days postpartum. Centrally, the vessels are of arterial type. Many have been completely obliterated. Others are recanalized. The spindle cells about the lumen will form the new media and adventitia. The wavy grey-white tissue at the periphery is the degenerated elastica interna of the old vessel.

Fig. 3.—(×80) The large vessel to the right is a thrombosed vein at the placental site. Note the meshes of fibrin arranged in dense bands or delicate fibers. To the left lies a partially closed artery. The internal elastic membranes of the old vessel is still recognizable. The central clot is poorly formed. Recanalization has begun.

clots (Fig. 4). Only occasionally was fibrin discernible, but platelets were not identified. Surrounding the large venous sinusoids were involuting arteries. More deeply in the section there were smaller veins which showed blood clot invaded by endothelial and fibroblastic cells. Fibrin was abundant. The remaining fragments of tissue were comprised of amorphous necrotic debris infiltrated with polymorphonuclear leucocytes. Occasional areas of regenerating endometrium were encountered.

Fig. 4.—(×80) Veins of the placental site. The distended vessels are filled with blood clot. Thrombosis is poor. Platelets and fibrin are lacking. The red cells are free.

CASE 2.—(No. AA166-528) a gravida iii, para iii, aged 35 years, delivered spontaneously after a labor of eight hours. After thirty minutes in the third stage, manual removal of the placenta was performed because of persistent bleeding. The puerperium was uneventful until the sixth postpartum day, when moderate bleeding appeared. This was seemingly controlled by a course of ergotrate. On the nineteenth postpartum day, however, profuse bleeding recurred. The cervix was found patulous, and the uterus was felt 4 finger-breadths above the symphysis. Curettage yielded several fragments of hemorrhagic tissue. The postoperative course was uneventful, and the patient was discharged on the fifth postoperative day. The pathologic report follows:

Several of the endometrial fragments were completely relined, the lining cells varying from low to medium columnar. The underlying stroma, however, was obscured by dense collections of lymphocytes and plasma cells. The component stromal cells were spindle, round, or fusiform. Other fragments, however, presented degenerating and hyalinized decidua at the surface, while the glands which lay subjacent were large and irregular. Their lining cells were low columnar, and the nuclei presented varying tints. The largest fragments were evidently derived from the placental site. The surface tissues overlying the muscle showed advanced necrosis, and in areas even the muscle cells were necrotic. Several veins lying near the surface presented degenerating hyaline walls (Fig. 5). A well-formed layered clot of red cells and platelets was present in the largest vein, but no fibroblastic invasion was seen

nineteen days after delivery. The smaller veins were surprisingly free from fibrin network, and the red cells appeared free.

It is apparent that in Case 1 clotting was initially poor. In Case 2 organization of the venous thrombi was delayed. Additional studies of normal postpartum uteri appear indicated for complete facts of normal thrombosis at the placental site.

Fig. 5.—(×40) Fragments from the placental site obtained by curettage. A large vein is surrounded by fasciculi of uterine muscle. The concentric layering of the clot is well shown. Thrombosis is adequate. The pale areas correspond to layers of platelets. Organization of the clot, however, is lacking on the nineteenth day following delivery.

(2) Recognition of abnormalities of decidual retention and separation as a factor in l.p.p.h. is due to the work of J. W. Williams.[11] In 50 uteri removed by cesarean hysterectomy, he demonstrated that separation of the placenta and membranes generally occurs in the spongy layer of decidua. The line of cleavage, however, was irregular, so that in some areas thick zones of decidua were retained. This confirmed a similar observation made by Kronig (quoted by Williams in 1901). A later study in 1931 on the postpartum uterus showed that necrosis of any retained decidua is complete by the seventh postpartum day, and that the subsequent detachment of the decidual slough is completed by the twelfth day. At this time the raw surface of the uterus is relined by cells proceeding from the fundi of the uterine glands. By the twenty-first day postpartum, the uterine endometrium has been completely regenerated, except at the placental site. Surprisingly, too, neither decidual nor endometrium infection nor the retention of fetal tissue interfered with regeneration, except at the placental site.

On this anatomic basis, l.p.p.h. can be ascribed to: (a) prolonged retention of normal amounts of decidua; (b) initial retention of excessive amounts of decidua. O. Fränkl[2] indicated that islands of decidua compacta retained in the uterus can proliferate. They become highly vascularized and bleeding proceeds from the "varicose vein plexus" opened during late separation of such decidual islands. Fränkl observed this lesion in six of 23 cases of late bleeding in which there was no other pathology. Küstner, who coined the term "deciduoma," confirmed this observation. Olshausen, Bumin, and others[12] presented similar findings (article by Normal H. Williams).[12] Our series, however, shows no instances of deciduoma, but there were three cases in which decidua was present beyond the twelfth day of the puerperium, a time when all decidua should have been normally detached and expelled. The remaining cases of late postpartum hemorrhage due to this factor must then be explained by the initial retention of abnormally large amounts of decidua. Separation of the membranes occurred at the surface and not through the spongy layer. Whether retained fragments of membrane are contributory, cannot be stated with certainty.

Our attention to the retention of excessive amounts of decidua as a cause of l.p.p.h. was focused by Cases 3, 4, and 5 in which large masses of decidual tissue were spontaneously expelled after an episode of bleeding (Table IV). In two other cases (1 and 2), sizable decidual masses were found in the cervix prior to curettage. All were clinically considered as cases of retained placental fragments until microscopic examination revealed their true character. When the remaining cases of l.p.p.h. without retained placental fragments were reviewed, it was significantly noted that in six of these patients bleeding occurred within the first ten days postpartum (during the time interval for spontaneous slough separation). The early onset of the bleeding and its relative mildness are significant clinical indications of the decidual factor.

TABLE IV. DECIDUAL GROUP

	SYMPTOMS			FEBRILE COURSE			THERAPY		
CASE NUMBER	ONSET OF BLEEDING IN DAYS	REPEATED EPISODES	FOUL LOCHIA	PREOPERATIVE	HIGHEST TEMPERATURE	POSTOPERATIVE	MEDICAL	SPONTANEOUS EXPULSION	CURETTAGE
1	Mod.-4th	0	0	1-3rd	101° F. 2nd	0	0	4th	4th
2	Mod.-7th	0	0	0	0	0	7th	7th	7th
3	Mod.-3rd	0	0	0	0	0	3rd	3rd	0
4	Mild-3rd	0	Yes	3-6th	101° F. 3rd	0	3rd	3rd	0
5	Mild-4th	0	Yes	2-5th	101.6° F. 2nd	0	4th	4th	0
6	Mod.-7th	1	0	0	0	0	0	0	9th
7	Mod.-13th	2	0	0	0	0	0	0	15th
8	Mod.-7th	0	0	0	0	0	0	0	9th
9	Mod.-8th	0	0	0	0	0	0	0	9th
10	Mod.-8th	0	0	0	0	0	8th	0	13th
11	Mod.-9th	0	0	0	0	0	9th	0	12th
12	Mod.-11th	0	0	0	0	0	11th	0	11th
13	Mod.-6th	0	0	0	0	0	0	0	6th

Grossly, the material recovered in these cases was noted as moderate but hemorrhagic. The large clotted vessels were prominent. Microscopically, as first described by Williams, the early decidua was infiltrated with blood, and the component decidual cells were necrotic or hyalinized (Fig. 6). In later stages the decidua was reduced to amorphous hemorrhagic debris infiltrated with neutrophiles. Only the recognizable hyaline shadow of occasional decidual cells allowed proper morphologic identity (Fig. 7). The vessels of sinusoidal type contained clot almost solely comprised of red cells. Platelets

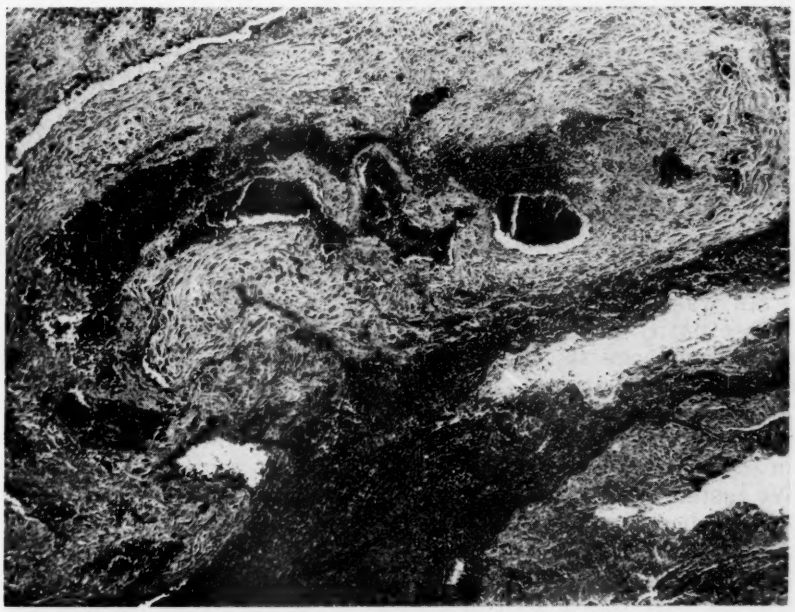

Fig. 6.—(×80) An elongated sinusoid filled with a poorly formed clot is surrounded by broad sheets of degenerating decidual cells. The latter are spindle or fusiform.

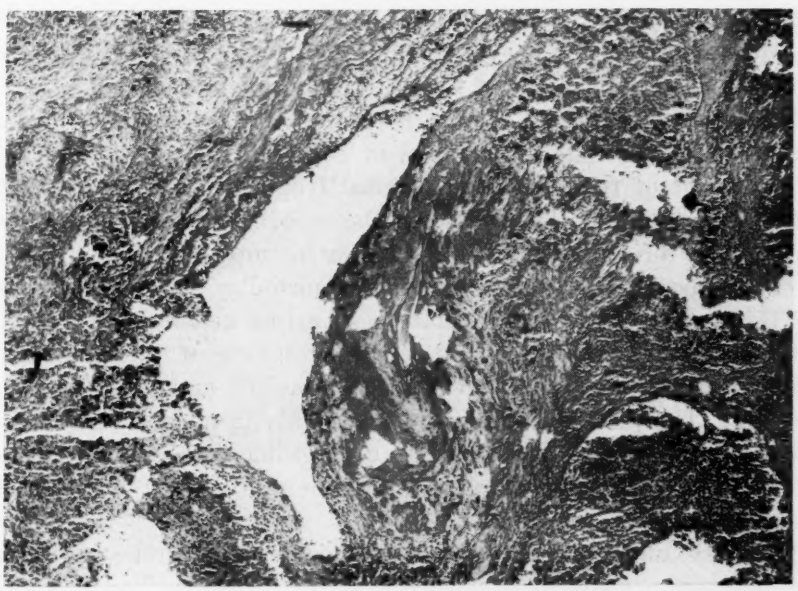

Fig. 7.—(×80) Segment of necrotic decidua. A large empty sinusoid is prominent. Immediately to the right is a zone of necrotic and hyalinized decidua. Isolated degenerating decidual cells are recognizable. In the right lower angle a poorly thrombosed sinusoid is seen.

were not recognized and fibrin was scant or lacking. Reopening of such poorly thrombosed sinuses during separation of the decidual slough with resulting hemorrhage appears well founded.

In the decidual group of 13 cases, the important clinical manifestations are indicated in Table IV. Nine patients were primiparas and four were multiparas. Seven were delivered spontaneously, while six required the use of forceps. The third stage of labor was without complication. In all instances there was spontaneous separation of the placenta followed by modified Credé. As expected from the physiologic considerations presented above, the bleeding as a rule presented within the first ten days, and in only two of the 13 cases did hemorrhage appear after the tenth day. Contrasted with "retained placental group," the bleeding was relatively mild, and shock was not encountered. Pain was not a symptom. The lochia was noted as foul in only two cases. Three patients showed mild preoperative febrile courses. Upon physical examination large shreds of tissue had been spontaneously expelled into the vagina in three patients. In two other instances, the decidua was loose and retained in the cervix. In all instances the cervix was patulous and the uterus was generally designated as subinvoluted. Medical therapy was employed in seven cases. Of these, three required no further treatment. In four of the five instances, where complete or partial expulsion of tissue was noted, ergotrate had been used. Ten cases were curetted. As a rule this therapy was instituted between the fourth and the fifteenth days. There were no postoperative reactions, and transfusions were only necessary in one case (No. 13). It is apparent that this group of l.p.p.h. is of mild type, and, if recognized, curettage may be avoided.

Conclusions

1. Retention of placental fragments is the most frequent cause of late postpartum hemorrhage. The retained fragment may be spontaneously expelled. More commonly, however, recurrent episodes of bleeding require surgical intervention. Formation of placental polypi is infrequent.

2. Digital exploration of the uterus is the only sure method of diagnosis; the other physical findings are insufficient.

3. Treatment of the retained placental fragment is surgical. Separation by the finger (curage) is the method of choice. If unsuccessful, the use of the curette or ovum forceps is safe. Such operative intervention for active bleeding in febrile cases is followed by moderate morbidity.

4. Uterine factors as causes of late postpartum hemorrhage have not heretofore been sufficiently emphasized. Noninvolution of the placental site is evidenced by poorly thrombosed veins which reopen and produce late secondary bleeding. The placental site requires restudy in normal postpartum uteri.

5. Retention of abnormal amounts of decidua vera during separation of the placenta and membranes is causative of the milder type of late postpartum hemorrhage.

6. Digital exploration of the uterine cavity is the first step in the treatment of late postpartum hemorrhage. Only by this method can a retained placental fragment be discovered and then removed. If no placental fragment is present, noninvolution of the placental site or separation of excessive amounts of decidual slough are the causative factors of the bleeding.

Thanks are herewith extended to the members of the Obstetrical and Gynecological staffs for permission to include their personal cases in this study.

References

1. Chiare and Robertson: in Siegel, P. W.: Handbuch Der Geburtsshilfe, Vol. 3, Munchen, 1920, J. F. Bergmann, p. 641.
2. Fränkl, O.: Arch. f. Gynäk. **129**: 87-96, 1926.
3. Goodall, J. R.: Am. J. Obst., N. Y. **60**: 921-985, 1909.
4. Eden and Lockyear: Gynecology, London, 1920, Macmillan Co., p. 428.
5. Hagstrom, H. T.: Am. J. Obst. & Gynec. **39**: 879, 1946.
6. Heyns, O. S.: South African M. J. **14**: 464, 1940.
7. Küstner, H.: Zeitschr. f. Geburtsh. u. Gynäk. **67**: 430, 1910.
8. Rutherford, R. N., and Hertig, Arthur T.: Am. J. Obst. & Gynec. **49**: 378, 1945.
9. Siegel, P. W.: Handbuch Der Geburtsshilfe, Vols. 3 and 4, Munchen und Wiesbaden, 1920, J. F. Bergmann, p. 41.
10. Williams, J. W.: Am. J. Obst. & Gynec. **22**: 664, 1931.
11. Williams, J. W.: Am. J. Obst. **16**: 336, 1917.
12. Williams, N. H.: West. J. Surg. **47**: 223-239, 1939.
13. Williams, I. W.: Obstetrics, ed. 8, New York, 1941, Appleton-Century Co.
14. DeLee and Greenhill: Practise of Obstetrics, ed. 8, Philadelphia, 1943, W. B. Saunders and Co.

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EXTRAPERITONEAL CESAREAN SECTION; INTRAPERITONEAL APPROACH

Presentation of the Author's Technique

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MUCH of the progress in the development of the lower uterine segment types of cesarean section has occurred in the past twenty-five years. The Waters' supravesical, the Norton paravesical extraperitoneal, and the Smith modification of the Veit-Fromme-Hirst exclusion transperitoneal cesarean sections, are striking examples of recent advances. Any operation which successfully excludes the peritoneal cavity is a step forward. The Smith operation, although safer than the intraperitoneal cesarean, two-flap type, in potentially infected cases, certainly cannot compete with the Waters' or the Norton truly extraperitoneal cesarean sections. In frankly infected cases, i.e., placental site infection, metritis, etc., no type of cesarean section is safe. This has been stressed again only recently by Norton. The Porro, modified as a total abdominal hysterectomy, is the operation of choice in these surely infected cases.

The Smith operation of peritoneal exclusion, although cleverly planned and executed, has some advantages and some disadvantages. While it does afford a more roomy and elastic area than some of the other exclusion operations, the area exposed is still too limited. It is more time consuming. The peritoneal apron is not intact; in fact, it is rather extensively cut. In the process of extracting the baby, the peritoneal apron is more likely to be further traumatized than it would be in those cases where the apron is left intact, i.e., Waters, Norton, Ricci, Latzko. The abdominal cavity must be excluded by a long line of sutures, all of which must perforate the peritoneal cavity which we had hoped to exclude. Furthermore, after the delivery of the baby, the suture line becomes quite distorted and allows for later seepage.

The present widely performed intraperitoneal, retrovesical, two-flap type operation has been so popularized that the low Sänger incision and the high classical incisions are rapidly becoming obsolete. Despite the greatly improved results obtained by this popularization of the intraperitoneal low cervical operation, it has certain disadvantages which can be eliminated. With this in mind, the writer proposes for consideration a type of cesarean section which aims to expose the retrovesical and infraperitoneal portion of the lower uterine segment by utilization of a small incision into the peritoneal cavity just above the abdominovesical reflection of peritoneum. Nothing of an original nature can be claimed for this method, since it utilizes principles already set down by Latzko, Ricci, Waters, Norton, and many others. It does, however, claim to be an improvement over the highly favored intraperitoneal lower segment operation which utilizes two flaps of peritoneum. The extraperitoneal enthusiasts claim that their techniques are not difficult to perform, yet, even in their expert hands,

the bladder has been cut, ureters injured, and the peritoneum buttonholed so frequently that their methods must be reserved for the obstetric surgeon who possesses better than average skill. The type of cesarean section here presented has served me well; the steps of the procedure are not difficult to perform; the operation can be mastered in a short time by the occasional operator; the procedure eventually familiarizes the operator with the exact anatomy of the pelvic fascias and the relationship and reflections of the overlying peritoneum so that when he is called upon to perform a truly extraperitoneal operation he will be better qualified; the operation, unlike the Waters' supravesical or the Norton paravesical extraperitoneal techniques, is a procedure that can be used electively in all patients who have not been in labor; the operation here recommended, while not intended to compete with the already almost perfect techniques of Latzko, Ricci, Waters, or Norton, can be kept truly extraperitoneal if the peritoneal incision is closed before the lower uterine segment is incised; and finally, it is claimed for this type of section: (1) relatively easy access is gained to the retrovesical, infraperitoneal area of the lower uterine segment, with less danger of repeatedly buttonholing the peritoneum, injuring the bladder, ureters, or any large vessels of the uterus; (2) the identification and exposure of the tonguelike fold of peritoneum is easy because it is at all times under direct visual control; (3) more room can be obtained by this technique than by any variety of extraperitoneal cesarean section so that the delivery of a baby of more than average size should be of no great concern to the operator; (4) that the technique herein described, if followed carefully, can be performed with ease, safety, and without the expenditure of too much time. The results, I believe, will be highly satisfactory, and it is my sincere hope that further experience in the hands of other obstetricians will prove me to be correct.

Technique

A midline incision is made in the abdominal wall extending from a point one inch below the umbilicus to the pubes. The recti muscles are dissected from their sheaths and retracted laterally (Fig. 1). The transversalis fascia and the peritoneum are incised vertically for about one or one and one-half inches; the lower end of this incision reaches a point about one-half inch above the parieto-vesico-peritoneal reflection. The peritoneal edges are grasped by forceps applied laterally (Fig. 2). The wound is spread out in a transverse fashion, as shown in Fig. 3. This raises the bladder somewhat and brings it more clearly into view. The peritoneum is then separated from the bladder, starting in the midline, proceeding toward the the left bladder angle, and finally, the right bladder angle is freed. This is done by sharp dissection in the midline and over the fundus of the bladder, where the peritoneum is usually very adherent. This part of the dissection is carried out under direct vision and it is made easy by one or two fingers within the abdomen (Fig. 4). These fingers lift up and put the peritoneum on a stretch. Once the fundus of the bladder has been freed of its peritoneum, it will be found that the peritoneum will now strip off the rest of the bladder with ease by using a gauze sponge until the vesico-uterine reflection of peritoneum is reached. This tonguelike fold of peritoneum which looks like a hernial sac must not be injured. This is, as Waters justly states, "the most important part of the entire operation." If desired, one may proceed, as in the Waters' operation, to denude the bladder of its fascia, which remains

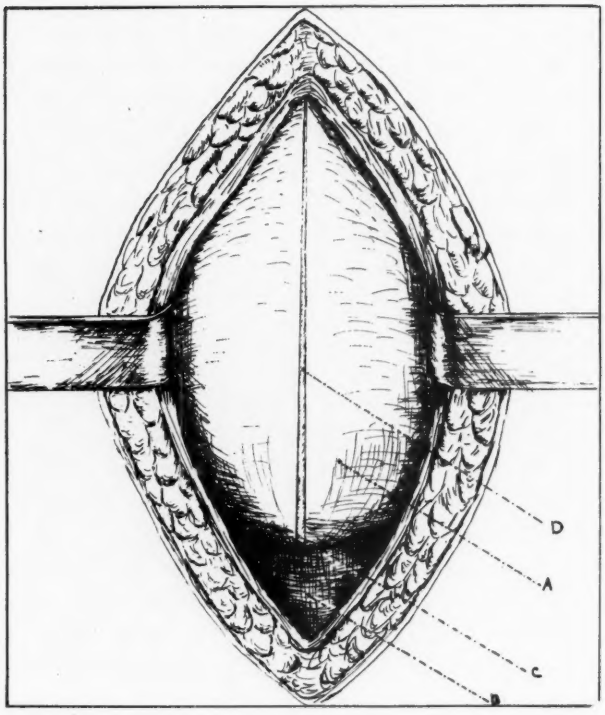

Fig. 1.—A-Transversalis fascia; B-bladder; C-parieto-vesico-peritoneal reflection; D-median umbilical ligament.

The recti muscles are retracted laterally, bringing to view the parietal peritoneum, fascia transversalis, and bladder. The urachus, shining in the midline, is seen to end at the apex of the bladder.

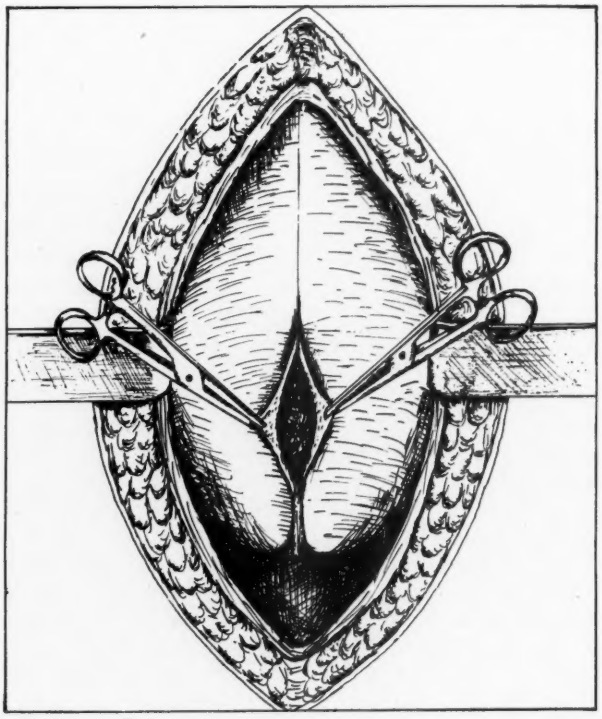

Fig. 2.—Incision of transversalis fascia and peritoneum. The edges are grasped with forceps.

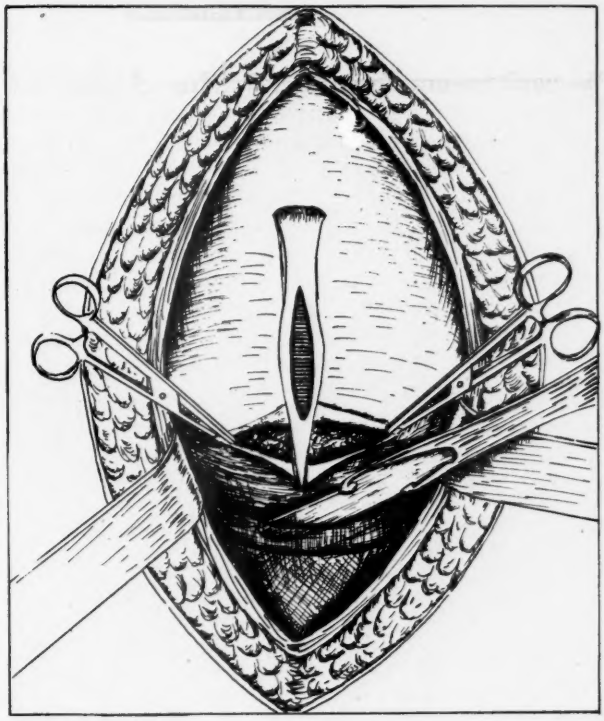

Fig. 3.—The wound is spread out in a transverse fashion. Thumb forceps can be used to elevate the lower edge of the wound. By sharp dissection with scalpel, the bladder is separated from its overlying peritoneum, starting in the midline, then proceeding to the left bladder angle and then to the right bladder angle.

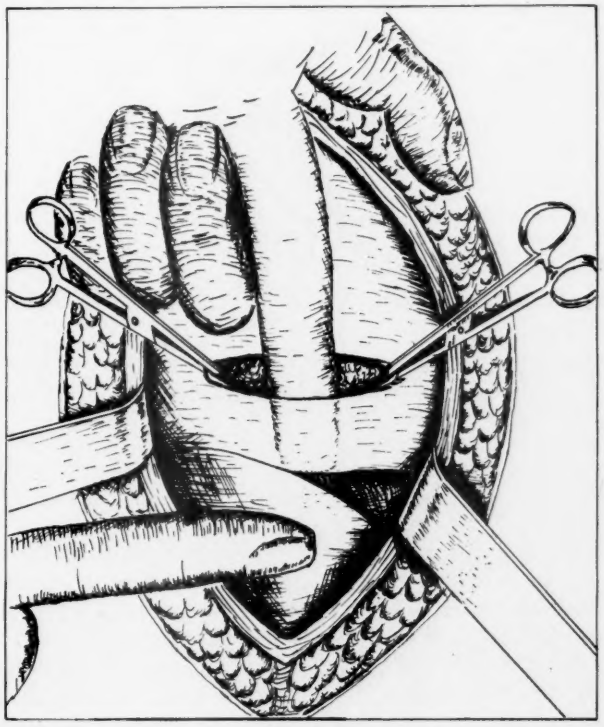

Fig. 4.—The bladder is pushed downward by the index finger of the right hand. As the strands of areolar tissue which join the vesical fascia to the peritoneum are brought to view by counter pressure with the index finger of the left hand within the peritoneal cavity, they are cut with scalpel or scissors. The top and right bladder angle is also denuded of its peritoneum.

attached to the peritoneum from the fundus of the bladder to the vesico-uterine pouch. If desired, one can also utilize the paravesical approach of Norton. Some men may choose to utilize a combination of the Norton, the Waters, or the above-described approach. However, the beginner must remember that there will be less danger of injury to the bladder, and that there will be less bleeding from the vesical vessels, if the peritoneum alone is dissected off. If some vesical fascia comes off during the dissection, it is allowed to remain attached to the peritoneum. The bladder is now pushed downward and to the right, exposing the fascia covering the lower uterine segment. This is incised about three-fourths of an inch inferior to the zone of peritoneal reflection. The incision of the lower uterine fascia should extend equally on both sides of the midline. It should be larger than the proposed lower uterine incision, and care

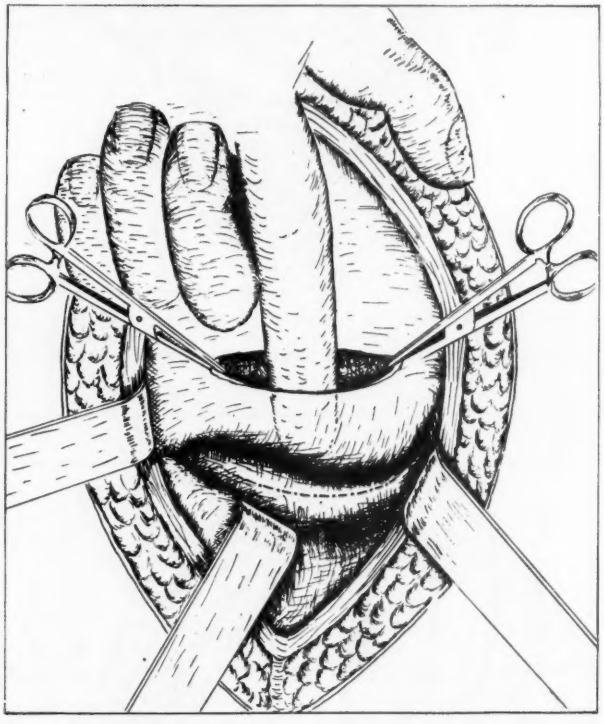

Fig. 5.—The bladder has been completely denuded of its peritoneum. The tonguelike hernial sac can be plainly seen throughout its course by inserting the index finger within the peritoneal cavity. By pushing upward on this fold and pushing downward and to the right on the bladder, the lower uterine segment covered with its fascia is seen. The type and position of the incision through the fascia is shown.

should be taken that only the fascia is incised (Fig. 5). A finger is inserted beneath the upper flap of fascia and bluntly dissected upward for a short distance, carrying with it the tonguelike peritoneal fold. The lower fascial flap is similarly pushed downward with the bladder. This incision of the uterine fascia over the lower uterine segment gives the operator increased mobility of the uterine peritoneum, and the bladder can be pushed downward with ease so that it will be out of the way. This incision also exposes a relatively large area of the lower uterine segment through which a central nick is made with the point of a scalpel about one inch above the detached bladder. With bandage scissors, this nick is enlarged in crescentic fashion, ends curved upward, starting from the left, then proceeding to the right. The ends of this incision may reach one and one-half inches above the apex of the curve. This incision should be large

enough to admit the closed fist with ease (Fig. 6). All retractors are now removed, and the baby extracted manually, by forceps or vectis, or by version and breech extraction, depending upon the choice of the operator. The writer prefers extraction by the breech in the vast majority of the cases. Ergotrate, $\frac{1}{160}$ grain, is given intravenously and the placenta extracted manually at once. The lower uterine segment is closed by three layers of continuous chromic catgut sutures No. 2. The bladder is anchored to its former position beneath the transversalis fascia. The peritoneal opening is raised in tent fashion and a plain catgut suture is tied around the base of the tented peritoneum. To secure this suture from slipping, the peritoneum distal to it is transfixed. This is done by

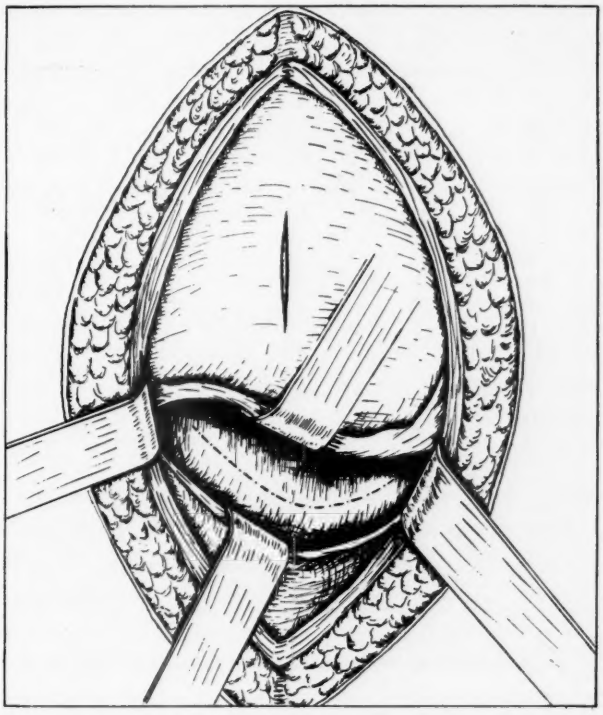

Fig. 6.—After incising the fascia of lower uterine segment, a finger is inserted under the upper flap of fascia, and, by pressure, this part of the fascia with the peritoneal tongue is raised off the lower uterine segment. A finger is inserted under the lower fascial flap pushing with it the bladder downward and to the right, exposing a fairly large space through which a crescentic incision is made.

passing the needle through the distal peritoneum from above downward and again from side to side. This procedure secures the first suture from slipping and has the advantage of closing off the peritoneal cavity without having any needle holes or sutures within the abdominal cavity. This closure of the peritoneum may be performed before the lower uterine segment is incised if the patient has been in labor, or it may be performed afterward in selective cesarean sections. The abdominal wall is closed by whatever method the surgeon prefers.

The primary purpose of this article is to describe the technical details of a new type of cesarean section which, I hope, will replace the highly popular two-flap type of cervical cesarean section. Although I do not like to tire the reader with statistics, it is fair to record my results in 19 cases, and then compare

these with 19 consecutive two-flap cesarean sections. Table I is a record of 19 low flap operations; while Table II is a record of 19 cesarean sections performed by the technique described. There were no fetal or maternal deaths in either group.

The operating time in the group in Table I averaged twenty-nine minutes. It will be noted that in two cases the operating time exceeded forty minutes. In Case 4, two subserous fibroids were removed. In Case 16, a tubal ligation was

TABLE I. RESULTS OF TWO-FLAP TYPE OF INTRAPERITONEAL CESAREAN SECTION

CASE	NAME	AGE (YR.)	OPERATING TIME (MINUTES)	DAYS IN HOSPITAL	MORBIDITY	DIS-TENTION	URINARY COMPLAINTS
1	E. O.	31	32	11	0	0	0
2	E. L.	35	30	13	0	0	0
3	M. C.	34	19	10	2 days	2 days	Unable to void —2 days
4	A. A.	32	47	11	1 day	2 days	0
5	M. B.	35	26	11	1 day	0	0
6	M. F.	29	35	11	0	0	0
7	M. G.	27	25	10	0	0	0
8	R. D.	30	27	10	0	0	0
9	L. P.	26	25	10	0	0	Unable to void —1 day
10	J. B.	27	23	10	0	0	0
11	A. C.	26	33	11	7 days	0	Burning on urination
12	A. M.	30	19	10	0	2 days	0
13	A. S.	24	23	12	3 days	0	0
14	S. M.	29	29	10	0	0	0
15	E. O.	33	27	11	0	2 days	0
16	A. M.	40	43	11	0	0	0
17	A. C.	25	34	11	0	2 days	Burning on urination
18	M. M.	33	27	10	0	0	0
19	C. L.	30	27	11	0	1 day	0

TABLE II. RESULTS WITH MODIFIED EXTRAPERITONEAL CESAREAN SECTION

CASE	NAME	AGE (YR.)	OPERATING TIME (MINUTES)	DAYS IN HOSPITAL	MORBIDITY	DIS-TENTION	URINARY COMPLAINTS
1	M. T.	26	29	9	0	0	0
2	A. F.	26	21	10	0	0	0
3	P. C.	29	35	10	0	0	0
4	E. M.	20	40	10	1	0	0
5	J. A.	24	33	10	1	0	0
6	M. C.	28	35	11	1	0	0
7	E. I.	26	35	9	0	0	0
8	P. N.	24	40	11	2	0	Unable to void —1 day
9	M. D.	29	40	9	1	0	0
10	A. Z.	20	40	10	0	0	0
11	A. C.	25	44	11	0	0	0
12	M. C.	34	35	10	0	0	0
13	M. B.	29	25	11	1	0	0
14	H. M.	34	45	9	0	0	0
15	C. M.	37	49	10	1	0	0
16	A. D.	26	32	9	0	0	0
17	F. O.	28	40	9	0	0	0
18	F. F.	30	32	10	0	0	0
19	M. S.	29	32	10	0	0	0

performed. In addition, tubal ligations were also performed on Cases 1, 2, 6, and 17. If we make allowances for the time consumed in performing these additional operations, the average time would be reduced to twenty-five minutes. The average hospital stay in Group 1 was 10.8 days. In this group, abdominal distention was seen in six patients and urinary complaints were present in four.

The operating time in the group in Table II averaged thirty-six minutes. It will be noted that in three cases the operating time exceeded forty minutes. In Case 11 a huge pedunculated subserous fibroid was removed. In Case 14, a large adherent chocolate cyst, the size of an orange, was removed from the right ovary. In Case 5, a bilateral tubal ligation was performed. If we make allowances for the time consumed in performing these additional operations, the average time would be reduced to thirty-two minutes. The average hospital stay in Group 2 was 9.8 days. Not a single patient of this group had postoperative distention and only one patient was unable to void for one day only.

Comparing the results of these two groups, we note that the operating time averaged thirty-two minutes in Group 2, and twenty-five minutes in Group 1. The extra time spent in Group 2 was more than compensated by the shorter hospital stay of one day, freedom from abdominal distention, and the almost complete absence of urinary tract complaints.

Advantages

1. Instead of making two separate peritoneal incisions, only one is utilized. The extent of the parietal incision will become minimal as the operator gains experience. When this incision is closed in the manner described, no raw surfaces, suture material, or needle punctures are present in the peritoneal cavity. This should minimize the possibility of postoperative adhesions.

2. The greatest danger of cesarean section is still infection. Seepage, when it does occur in the intraperitoneal cervical cesarean section by the flap method, must still be into the general peritoneal cavity. By this method, seepage or uterine wound breakdown will be extraperitoneal.

3. At no time during the operation does the bowel come into view. Sponges in the abdomen are therefore unnecessary, hence eliminating the possibility of postoperative distention.

4. A careful checkup of all cases after the uterine wound has been closed to determine the possibility of peritoneal contamination by spill of blood or amniotic fluid revealed that practically no fluid had entered.

5. The cervical wound can be placed low enough, i.e., two inches below the point of reflection of the vesico-uterine peritoneum. This makes the operation a truly cervical one and not a low fundal one as I have seen it done many times. The wound is thus placed in that portion of the uterus that is noncontractile and hence is more likely to be at rest. The wound is thus placed in that portion of the uterus which stands infection best.

6. This operation can be used routinely in place of the low-flap method, regardless of whether the patient has been or has not been in labor, and also regardless of how deeply the vesico-uterine fold of peritoneum extends behind the pubes. This is a highly desirable advantage.

7. This familiarity with the anatomy of the cervical and vesical fascias and with the vesico-uterine septum gives the operator added confidence when he is

called upon to do a Latzko or a Waters operation in frankly infected or neglected cases.

8. This operation is not intended to replace the Latzko nor the other strictly extraperitoneal operations, which are technically more exacting to perform and unquestionably safer than any type of operation in which the peritoneal cavity is opened. However, it does enable the operator to perform ligation of the tubes and allows him to inspect the uterus and adnexae without detracting from the merits of the operation. This advantage is missing in the extraperitoneal operations.

9. The amount of space available for the delivery of the baby is decidedly greater by this method than by the Latzko, the Waters, or the Norton operations. In fact, it gives as much space as is available in the intraperitoneal, two-flap type, cesarean. At no time should the operator have to resort to the use of forceps to deliver the head because of restricted space. It has been my practice to do routine internal podalic version on all vertex cases to deliver the babies. The uterine wound will not tear, as a rule, if the initial incision into the lower uterine segment has been made large enough, i.e., large enough to easily admit the closed fist.

10. The amount of time necessary to perform this type of operation should not exceed that taken to perform an intraperitoneal, two-flap type, by more than five minutes. It should not take over thirty to thirty-five minutes.

11. There is less danger of injuring the bladder or of repeatedly buttonholing the peritoneum because the separation of the bladder from the peritoneum is aided by counter pressure of the internal fingers. The dissection is at all times under direct vision. There is never any need to guess where the vesicouterine fold or tongue of peritoneum is located. It can be easily seen at all times. It is not necessary to distend the bladder with methylene blue solution. In fact, the operation can be more easily performed when the bladder is collapsed.

This simple modification of the cervical cesarean section by eliminating the use of flaps, is, I believe, a distinct improvement, and I feel that this method has much to offer those who care to perfect themselves in its performance. I have no doubt that other obstetricians have done this operation in some modified form, but when the above technique is followed and tried by different surgeons, I believe it will be preferred by many as the operation of choice in elective cesarean section.

THE SURGICAL TREATMENT OF PHLEBOTHROMBOSIS IN OBSTETRIC AND GYNECOLOGIC PATIENTS*

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BEFORE discussing the treatment of phlebothrombosis as it occurs in obstetrics and gynecology, it is wise to define the two types of lesions in the veins as met with in the above-named specialties.

1. *Thombophlebitis.*—Thrombophlebitis, as the name indicates, is a phlebitis and periphlebitis sometimes associated by an absence of a clot in the lumen. It is usually initiated with a chill, high temperature, swelling of the leg, marked tenderness, and often redness over the course of the involved veins. It is characterized very largely by a perilymphatic involvement as well as involvement of the walls of the vein. Embolism following thrombophlebitis is relatively rare. It occurred in 10 per cent of the Toronto series, and in about 12 per cent of the cases analyzed by the Mayo Clinic.

2. *Phlebothrombosis.*—Phlebothrombosis is characterized by a blood clot which fills the lumen of the vein. The onset may be sudden. It is not accompanied as a rule by as high an elevation of temperature nor with as great swelling of the legs as in thrombophlebitis. Homans has shown experimentally that if one wishes to create the so-called "alba dolens" in experimental animals, it is necessary to destroy the lymphatics. Mere ligation of the vein will not, as a rule, create swelling.

Frequently, the diagnosis is not made until a pulmonary embolism has been discovered. I believe that in gynecology and obstetrics, the diagnosis of phlebothrombosis is much more difficult than it is in general surgery. In the general surgical patient, the thrombus usually starts in the deep veins of the calf. The following clinical findings will make one suspicious that thrombosis is present and that embolism may occur:

Homans has drawn attention to the fact that the greatest danger of thrombosis and embolism lies in the deep veins of the calf, and that if the foot is hyperextended, causing extension of the gastrocnemius, the patient often complains of pain in the calf, whereas lying normally, he is unaware of it. Also, I have found by comparing the two calves, with the knees in semiflexion and the patient on his back, that the affected leg gives one an impression of more resistance in compressing with the fingers the gastrocnemius muscle against the posterior surface of the tibia. Any swelling of the thigh is more easily detected, as usually the patient complains of some tenderness in the region of Poupart's ligament. Careful palpation will reveal a pencil-like cord behind the femoral artery. These clinical signs are well worth noting in patients with unexplained temperature.

On the other hand, in obstetrics and gynecology, the thrombus very frequently starts in the pelvic veins, and emboli may occur before there is any manifestation of thrombosis in the extremities.

*Read (by invitation) at a meeting of the New York Obstetrical Society, May 14, 1946.

One patient I saw developed a phlebothrombosis secondary to a degenerating fibroid. Thrombectomy was performed, and two weeks later a hysterectomy was performed. At the time of the hysterectomy, the surgeon noted that the iliac vein was free from any thrombosis, whereas the pelvic veins coming from the uterus showed definite evidence of phlebothrombosis.

Another patient had a normal delivery. Twelve days later, she developed a phlebothrombosis of the left leg. The femoral vein was exposed; a clot was sucked out well upward into the pelvis. Free bleeding occurred. Her temperature and pain immediately subsided, and the patient went home. Four weeks later, she had an attack of phlebothrombosis in the right leg and was returned to the hospital. A clot was sucked out of this leg and the femoral vein was ligated. It does not seem likely that, during this period, there was a residual clot that extended upward into the vena cava, as the patient had had no pain, no tenderness, and the swelling in her left leg had completely subsided. There must, however, have been an extension from the pelvic veins of the uterus, which created the second attack.

These observations occurring in phlebothrombosis in women who are pregnant, or secondary to hysterectomy, have made me alter my plan of attack somewhat, as I shall describe later when we come to the problems of treatment. I will state now, however, that I believe in cases of embolism occurring in gynecologic or obstetric conditions, the femoral vein should be exposed and the emboli sucked out higher up in the pelvis, even if there is no evidence of thrombosis in the femoral vein.

Before discussing the individual problems that occur in obstetrics and gynecology, I should like to review very briefly the use of anticoagulants. There are three main anticoagulants now in use:

Sodium thiosulfate.—In 1928, at the Fifth Avenue Hospital, Dr. Stanley-Brown and I began our early experimental work on thrombosis and embolism, and we were looking for an anticoagulant which might be given as a therapeutic measure to prevent thrombosis and embolism. We consulted Dr. Charles Loeb, who was professor of pharmacology at Columbia University, and he suggested sodium thiosulfate. He had used it in dogs to prevent extra corporeal clotting. We didactically started to use the routine injection of sodium thiosulfate. Since that time, considerable experimental work has justified our impression that it had anticoagulant properties. The possible rationale for the use of sodium thiosulfate is described by Jorges and Bergstrom, who state that the anticoagulant activities of different heparin preparations obtained in a similar manner from the liver vary in their sulfur contents. Preparations of liver heparin containing from 7 to 12.26 per cent of sulfur show anticoagulant potencies varying from 45 to 160 per cent of the standard heparin from which they are derived. Heparin is largely produced by the mast cells in the intima of the blood vessels, and it is possible, therefore, that the sulfur element of sodium thiosulfate may increase the anticoagulant activities of the heparin which is liberated in the blood stream.

In a large series of cases at the Fifth Avenue Hospital, we were able to show that we had diminished the incidence of thrombosis and embolism in cases where we suspected that there might be an accident. Our suspicions at that time were based on the increased prothrombin and fibrinogen in our routine studies

of the blood clotting factors. Since that time, it has been my custom to use sodium thiosulfate whenever a patient has been moderately distended, whenever there is a continued slight elevation of temperature, and whenever I fear an accident. In cases so treated, I have never had thrombosis or embolism develop. It is my custom to inject 10 c.c. of a 10 per cent solution of sodium thiosulfate intravenously for several days in succession. The drug is cheap, apparently it has no toxic effect, and it is not particularly annoying to the patient.

Heparin.—If thrombosis has occurred, I do not believe that sodium thiosulfate compares in any way with either heparin or dicoumarol. You are all aware of the continuous intravenous therapy with heparin. You know its expense, the difficulties to the patient of having a continuous intravenous solution during several days, and the dangers of hypoproteinemia from too much intravenous fluid. If heparin is given intravenously, it has to be given continuously, because its anticoagulant effects cease within two or three hours after the injection has been discontinued. Patients have been seen who have developed thrombosis or embolism following the discontinuance of the use of heparin.

Recently, a newer method for heparin treatment has been developed by Loewe. I should like to describe his method of using heparin subcutaneously by injections at two- to three-day intervals. I quote from Loewe as follows: follows:

"To accomplish a slower and more equitable absorption of heparin, the Pitkin menstruum was adopted as a vehicle. This menstruum was developed to regulate the rate of release of water-soluble drugs injected intramuscularly or subcutaneously. The ingredients are gelatin, 15 to 30 per cent; dextrose, 5 to 12 per cent; acetic acid, 1 to 1.5 per cent; distilled water, as much as will suffice to make 100 per cent. The viscosity of the menstruum, which is predicated on the concentration of the gelatin and dextrose, determines the rate of liberation of the drug; the greater the viscosity, the slower the liberation. In the preparations containing heparin, the optimum percentages of gelatin and dextrose were 18 per cent and 8 per cent, respectively.

"Ampules containing varying proportions of heparin and Pitkin menstruum, with or without vasoconstrictor elements, were prepared. All ingredients apart from heparin were found to be inactive in control tests.

"The contents of the ampules were liquefied at 110° F., drawn up through a 2.5-inch 19-gauge needle into a previously warmed, sterile 5 c.c. or 10 c.c. syringe and immediately injected subcutaneously, preferably in the anterior or lateral aspect of the thigh. Intragluteal injections were also done in a limited number of instances. Although this method of administration was abandoned because of too rapid absorption, further experience may eventually prove it to be just as effective as by the subcutaneous route. When two ampules were employed, the contents were thoroughly admixed in the syringe before injecting. The material congealed promptly following inoculation. The injections were administered with a minimal amount of discomfort to the patient. Some patients subsequently complained of pain, tenderness, and swelling at the site of inoculation, particularly when a large amount (3 to 4 c.c.) of the menstrum was used. This, however, did not prove to be a deterrent to further treatment, and symptoms promptly subsided upon cessation of therapy."

My observations of Loewe's method show that it does lengthen the bleeding time, and that the patient has no ill effects from the treatment save for the pain in the injection area. This tenderness in the area where the heparin-Pitkin solution is injected becomes quite a problem, as the patient may, about the time of the third injection, oppose the injection because of the pain involved. As the process is improved, however, I feel certain that this one difficulty will be remedied. To those who have had to give heparin constantly for from five to ten days, this method is a great improvement. The expense of the old method, and the amount of fluid given during each 24 hours, almost make continuous injection prohibitive in these days of diminishing nursing care.

The results of Loewe's treatment are that it is possible now to heparinize a patient for ten days at much less expense and with possibly three to four subcutaneous injections during this time.

Dicumarol.—This is a compound which occurs in spoiled sweet clover silage, and it was discovered in the study of sweet clover diseases which caused the hemorrhagic diatheses in cattle from the ingestion of spoiled sweet clover hay.

Link and his co-workers completed the isolation and synthesis of dicumarol in 1940. Lately, it has been used in various clinics as a possible substitute for heparin. It has the advantage that it is relatively cheap, that it can be given by mouth, and that it produces a prolongation of the prothrombin and coagulating time. Its disadvantages are that it takes from twenty-four to thirty-six hours before it begins to show its anticoagulant effect, and that the action may continue several days after the drug itself has been discontinued. Experimental study shows that it causes a widespread dilatation of the superficial vessels but no lesion of the vessel walls, and does not create liver necrosis.

Dicumarol is being used more and more extensively by all observers. It has disadvantages in that it is hard to control if hemorrhages should occur following its use. However, Willard Parsons has recently reported the control of the hemorrhagic tendencies following the use of dicumarol by administration of vitamin K. If this is possible, it makes the drug much safer. Previously, it has been thought that only transfusions would in any way control its hemorrhagic tendencies.

Prophylactically, dicumarol is given in many clinics and, so far, with many promising reports. In my own experience, I have never seen a case of thrombosis or embolism occur after the use of intravenous sodium thiosulfate when administered prophylactically. I think it is less dangerous and more controllable.

Treatment

During pregnancy, there are patients who develop either localized subcutaneous attacks of thrombophlebitis in the veins in the calf, or the process may extend upward along the long saphenous vein. These attacks occur frequently in patients who have had varicose veins before they become pregnant. I believe that in these patients, a proximal ligation of the long saphenous vein, which may be done under local anesthesia either at home or in the hospital, may save the patient considerable distress and some danger at term. It is interesting to note that if a segment of vein is taken out, the pain almost immediately disappears in the involved vein, often quite a distance distally from

where the vein is ligated. In cases where women suffer from migatory phlebitis or from recurring attacks of phlebitis, particularly where it is superficial in the veins of the calf, it is well to look between the toes to be sure there is no epidermiphytosis. This is a frequent cause of recurrent phlebitis. Irving Wright in New York believes that it is probably due to a virus, while Miller, who works in New Haven, believes that it might be allergic in character, it is a cause of constant recurring phlebitis, and an attempt should be made to clear up the epidermophytosis. Frequently, we do not think to look between the toes in these patients.

The obstetrician is frequently faced with this problem: The patient has had phlebothrombosis in a previous pregnancy, and is this likely to recur in the following one? What prophylactic measures should he institute?

If the previous pregnancy has been complicated by a phlebitis of the long saphenous vein, proximal ligation may be advisable. If it was accompanied by a deep femoral phlebitis, dietary measures and the use of anticoagulants pre-partum and after five or six days post partum may be of great help. It is hard to evaluate how much help these prophylactic measures are, because often a patient has had phlebitis in the first pregnancy, and has not had any in later pregnancies without any prophylactic therapy. My suggestion, however, would be that 5 or 6 days before delivery, sodium thiosulfate should be used intravenously; and after five days post partum, in order not to increase postpartum bleeding, either sodium thiosulfate or dicumarol can be administered. The same method of approach may be used in gynecologic patients who are forced to have an operative procedure and have had a previous history of phlebothrombosis either following pregnancy or after a previous operation.

Treatment After Phlebothrombosis Has Been Recognized Post Partum or Postoperative.—There are three therapeutic measures which may be used, and they are:

1. Proximal ligation or thrombectomy.
2. The use of anticoagulants.
3. Injection of the first, second, third, and fourth lumbar ganglia as described by Leriche and Ochsner.

Proximal Ligation or Thrombectomy.—It is only fair to state before I begin the discussion of the treatment of phlebothrombosis, particularly when there has been an antecedent embolism, that I am strongly in favor of the operative approach and I shall attempt to give my reasons during this discussion.

The term proximal ligation means that one is able to ligate the vein proximal to the location of the thrombus, and thrombectomy means that if the femoral vein or the long saphenous vein are exposed just below Poupart's ligament and the clot extends upward into the iliac vein, the vein is opened and the clot is removed by suction until free bleeding occurs.

I believe there is very little discussion about the problem of proximal ligation. We will agree that this is feasible and that very little risk is entailed, and I shall not make any analysis of the cases that I have done this procedure on, except to state that I have had no mortality following its use.

The problem of thrombectomy is readily open to debate. One may ask the following questions in considering thrombectomy:

1. Is there not danger in removing the clot of breaking off the clot and having it extend upward into the vein?

Yes. In the 20 cases on which I have performed thrombectomy, I have had one patient who, during the process of sucking out the clot, became a little short of breath and looked a little cold and sweaty. The next day, however, his chest signs were negative and he was in no respiratory distress, but I am fairly con-

fident that a small piece of thrombus did ascend upward into his thorax. In no other case have I seen any evidence of any such occurrence.

2. Will not the thrombus recur above where the ligation has been performed?

In order to prevent this occurrence, it has been the custom of Homans and others to administer anticoagulants after the thrombectomy. On the other hand, Allen and his group, working at the Massachusetts General, have not used anticoagulants as a routine and have not had any severe recurrence of thrombosis after ligation and thrombectomy.

3. Is there a residual swelling of the leg following ligation of the femoral and long saphenous veins?

In the large majority of cases, there is no residual swelling. I have had two patients who had persistent swelling two to there months postoperatively. One of these patients is now actively playing tennis, so that I know the swelling has largely decreased. The other patient, a recent case, had very marked swelling for three weeks postoperatively. He had a hematoma in his incision and a moderate amount of inflammatory process, which I believe interfered with his lymphatic drainage. Recent reports from his doctor state that this swelling has markedly decreased. If it should persist, I believe that lumbar sympathetic block would hasten the disappearance of the edema.

I should like to review briefly the cases on which I have performed thrombectomy in gynecologic and obstetric cases. I have performed two preoperative thrombectomies in preoperative gynecologic cases. I have performed two thrombectomies in postoperative gynecologic cases, and three in obstetric post partums. I should like to review these histories briefly and then analyze my impressions after this small series of cases:

Case 1.—A 68-year-old female, with a large ovarian carcinoma, had evidence of a thrombus in her right femoral and saphenous veins. At the time of operation, a thrombus was removed from her right iliac vein, and then a bilateral oophorectomy for tumors the size of a football was performed. She died on her fifteenth postoperative day from renal failure. There was no residual swelling of the leg or signs of pulmonary condition. No autopsy was obtained.

Case 2.—A woman, 46 years of age, had been seen by a gynecologist, who recommended hysterectomy for an extremely tender uterine fibroma which was fixed in the lower portion of the pelvis. The uterus extended midway to the umbilicus. Ten days later, while awaiting operation, acute phlebothrombosis occurred in the left femoral vein. I was called to see the patient at this time. There was no evidence then of pulmonary embolism. It was felt, however, that this patient would need hysterectomy in the near future because of a degenerating fibroid, and that it would be advisable to be sure that the clot was removed from the iliac vein. The clot was sucked out from the left iliac vein, and she was treated postoperatively by subcutaneous injections of heparin. Two weeks later, while still under heparinization, a supracervical hysterectomy was performed. The iliac vein was palpated and there was no evidence of any clot in its lumen. There were, however, some old thrombi in the veins of the broad ligament. This patient's convalescence was uneventful. She left the hospital two weeks after the hysterectomy.

Case 3.—A woman 53 years of age had had a supravaginal hysterectomy performed by another surgeon four weeks previously. For the previous two weeks before I saw her, she had had pulmonary embolic seizures, confirmed roentgenologically, and by Dr. James Miller and Dr. Harold Hyman. There

was fluid at the right base. The left calf and thigh were moderately swollen. She was operated upon. Under local anesthesia, the femoral vein was exposed. It was occluded with clot, but the long saphenous vein was not involved. The clot extended upward about 7 inches in the iliac vein. The same operative procedure was carried out, but, in addition, she had a lumbar ganglion block with novocaine. She had a moderate infection of the fat at the operative site in the thigh. She was given heparin subcutaneously by Loewe's method. Her convalescence was uneventful, and she had no residual swelling.

CASE 4.—This patient had a supracervical hysterectomy three weeks previously. During the past week, she had had three definite small pulmonary emboli. The left femoral vein contained a thrombus extending well above the inguinal ligament. A long thrombus above Poupart's ligament was removed by suction. She was treated by subcutaneous heparin. She had some residual pain in the leg for three weeks. The swelling in the thigh and leg rapidly subsided.

CASE 5.—This patient had a normal delivery of a child on April 19, 1944. On April 25, swelling was noted in the left leg and thigh, and she had an attack of pain in the chest on May 9. The patient was kept in bed and treated with rest. On May 15, pain and swelling appeared in the right leg, and the patient had another attack of pain in the chest. Under local anesthesia, both veins were exposed, and a clot was sucked out of each long saphenous and each femoral vein. Heparinization was administered for five days postoperatively. Convalescence after this was uneventful, save that she had considerable swelling of both thighs, which persisted for six weeks. In a late follow-up, I have learned that she is playing tennis, and, therefore, it is obvious that the swelling must have become greatly reduced.

CASE 6.—(See case report by R. S. Millen, this issue, p. 118.) At the first operation, I am sure that I had not sucked out the entire clot because I had not obtained adequate bleeding. The patient was extremely nervous, and it so happened that the tube supplied did not allow adequate suction for the removal of the thrombus. I have always felt that if I had been successful in the complete removal of her thrombus, the later sequelae might not have developed. When the thrombus developed in the right leg, I was confident that complete removal had not occurred, and the post mortem confirmed this observation.

CASE 7.—A young woman had a normal delivery, and, after her tenth postoperative day, developed a phlebothrombosis in her left femoral vein. The vein was exposed, the clot was sucked out, and free bleeding occurred. She went home a week after this procedure, and three weeks after she had been home, she developed phlebothrombosis of the right leg, and this clot was removed by another surgeon. Her convalescence in this case was uneventful.

Allen and his associates believe in the bilateral approach in all cases of phlebothrombosis. There is a certain amount of risk in the bilateral approach, because in sucking out the thrombus from one vein, one is likely to suck out more blood than one realizes, and bilateral approach might tend toward exsanguinating the patient. After analysis of the complications in general surgery and in obstetrics and gynecology, I am impressed with the fact that many of the thrombotic processes originate in the veins of the broad ligament, and that to successfully treat a gynecologic or obstetric case, if the patient will stand the procedure, a bilateral approach is the best procedure. Where the complication occurs as the result of some general surgical process, I believe that the treatment

of the involved side is sufficient. I have had no cases that occurred as a complication of general surgery, such as gall bladders, hernias, etc., that have needed bilateral ligation or where a second surgical procedure on the other side had to be done.

Conclusions

Lumbar sympathetic block has been popularized by Alton Ochsner and his associates in the treatment of venous occlusion in the extremities. Certainly in thrombophlebitis, with elevation of temperature, where there is not much risk of embolic formation, this procedure relieves pain and hastens the convalescence of the individual. On the other hand, where phlebothrombosis is present and there is danger of pulmonary emboli, it is my firm conviction that the operative approach and ligation of the vein is safer than relying upon the use of anticoagulants or lumbar sympathetic block. While Murray and others have reported excellent results from the use of anticoagulants without operative interference, I think that the convalescence of the patient is safer and shortened by either proximal ligation or thrombectomy. Many of us have seen emboli occur shortly after the cessation of heparin therapy.

Allen, Arthur W.: Thrombosis and Embolism, Bull. New York Acad. Med. 22: 169, 1946.
Homans, J.: Deep Quiet Venous Thrombosis in the Lower Limb, Surg., Gynec. & Obst. 79: 70, 1944.
Leriche, R., and Kunlin, J.: Traitement immediat des phlebitis post-operatoires par l'infiltration novocainique du sympathique lombaire, La Presse Medicale 42: 1481, Part 2, 1934.
Loewe, L., and Rosenblatt, P.: A New Practical Method for Subcutaneous Administration of Heparin, Am. J. M. Sc. 208: 54, 1944.
Murray, D. W. G., and Best, C. H.: Heparin and Thrombosis: Present Situation, J. A. M. A. 110: 118, 1938.
Ochsner, A., and DeBakey, M.: The Therapy of Phlebothrombosis and Thrombophlebitis, Arch. Surg. 40: 208, 1940.

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ADVANTAGES OF SURGICAL TREATMENT IN PHLEBOTHROMBOSIS*

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I HAD occasion to see several cases within a short period of time in the fall of 1944 and was fortunate enough to have been able to obtain the help of Doctor F. W. Bancroft in the treatment of these patients. In view of the fact that he is presenting the paper of the evening on this subject, I will avoid any discussion of the anatomic approach to the operation, the advantages or disadvantages of the different types of heparin therapy, such as dicoumarol, intravenous heparin, or that given intramuscularly, and will merely state briefly the salient features in the case reports to illustrate the advantages of surgical treatment.

CASE 1.—Mrs. J. P. developed a femoral phlebothrombosis ten days after an easy, early, complete abortion at home. At the end of an afebrile week she was instructed to get out of bed, and active medical care was discontinued. However, she obtained a supply of seconal from a nurse friend and remained in bed. One week later she notified her family doctor that her leg had been swollen for several days. I was then informed of its occurrence and arranged for a consultation with Doctor Bancroft. A diagnosis of femoral phlebothrombosis was made, but, in view of the length of time since the onset of the swelling and the fact that the patient was at home, it was decided not to operate. She was kept in bed another eleven days. Eight days later, or twenty-six days after the onset, her leg was normal in size as long as her activity was limited to that necessary for minimal bathroom requirements. Some months ago, when examined, there was no swelling at all, even with exercise.

CASE 2.—Mrs. G. W. was delivered by another obstetrician at the Nassau Hospital. On her eighth postpartum day she began to have swelling of her left leg. Seven days later there was swelling of her right leg. The swelling started to go down six weeks later while she was still in the hospital. She was first seen by me eight and one-half weeks after the onset of her thrombophlebitis when there was still some swelling. She was turned over to Doctor Bancroft who advised continuance of the medical regime because of the long history. I understand that fourteen weeks later she was still having some pain and swelling in both legs on activity and was confined principally to her bedroom and bathroom.

The day following the consultation first mentioned, the same internist had Doctor Bancroft see another patient, Mrs. R. B., with phlebothrombosis, who had been under observation for menorrhagia at the North Country Community Hospital in Glen Cove for twelve days. The patient's left leg was definitely swollen, both in the thigh and in the calf. Doctor Bancroft removed an organized adherent clot from the left femoral vein, which vein was then cleared by suction with a cannula which was passed up to the bifurcation. The patient was also treated with heparin intravenously by a slow continuous drip for twenty-four hours, and during the following six days by intramuscular injections. She was out of bed in one week, and five days later a complete hysterectomy was performed by Doctor Corscaden of this Society. There was no sign of thrombi

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in the pelvic veins at operation. Fifteen days later she was discharged with no apparent increase in size of the left leg. Some months following the operation a study revealed no increase in size of the left leg and full activity of the patient.

CASE 3.—Mrs. E. R. was operated upon at the North Country Community Hospital six weeks before term for a premature separation of the placenta. A living child was obtained and, after a normal postpartum course, the patient went home in good condition on her eleventh day. Two days later she began to feel a pain in her chest and was readmitted to the hospital with a suspicion of its cause being due to an embolus. However, examination revealed no evidence of any swelling in either leg, and the internist who had referred the case to me made a diagnosis of virus pneumonia, both by physical examination and x-ray studies. Daily investigation revealed no signs of phlebothrombosis until the tenth day of her readmission. That day Doctor Bancroft opened the left femoral vein under local anesthesia, due to the patient's pulmonary condition (since x-ray showed lesions in both lungs), and the patient's extreme nervousness and pleading against a general anesthetic. It was still thought that this patient's primary condition was virus pneumonia and that the phlebothrombosis was secondary to the enforced bed rest. Considerable pain and discomfort to the patient were encountered in this procedure and, although the clot was aspirated and a fairly good flow of blood was obtained, going over this case later by comparison with the other two cases operated upon, there was not the same vigorous back flow of venus blood. This patient was treated with intravenous and intramuscular heparin for one week, during which time no further chest symptoms were noted. Her temperature started to go down, and after several days she was allowed to sit out of bed, as it was felt that the virus pneumonia would not permit her temperature to go completely down and that it would be better for her to have a small amount of activity, rather than to keep her immobilized too long. The patient seemed to be improving, when suddenly she was again taken with an episode of pain in the chest, inability to breathe, etc. More râles were encountered in the chest on the right side where they had originally occurred. The left side by this time had cleared up to a marked degree. The patient was then kept in bed with some leg exercises. However, several days later swelling occurred in the right leg with tenderness over the right femoral vein. Doctor Bancroft operated this time under a spinal anesthesia which was given with particular care not to flex the thigh at the hip joint so as to in any way dislodge the clot. However, shortly before the patient was lifted from the stretcher to the operating room table she complained of a peculiar smell. It was felt that this might be largely due to the severe nervous strain that the patient was under and the operative procedure was carried out without any undue difficulty after 50 mg. of spinal anesthesia had been given. The operation was easily done and a very vigorous back flow was obtained. However, the patient's general condition was quite poor and she died thirty-six hours later. Postmortem examination revealed a complete obliteration of the right main pulmonary vessel and a partial obliteration of the left, so that she was only breathing with a small portion of the upper lobe of the left lung. The lesion in the left lower branch was old and well organized. That in the right contained an old and well-organized clot with a more recent one. This one probably occurred just before her second operation was done. There was definite involvement of the hypogastric veins, and there was no question but that the etiology of her chest condition all along had been emboli from a thrombophlebitis of the hypogastric veins, following her cesarean section.

I feel the failure in this case was not due to the surgical procedure, but perhaps to the selection of the anesthetic. Intravenous pentothal might have enabled

a more thorough and less painful procedure and all the clot might have been removed. Also, by using hindsight it would have been wiser to have done both sides at the first operation.

The third case treated by surgery (Case 4) illustrates the advantage of the procedure to obstetric patients.

CASE 4.—Mrs. B. C., having been out of bed for several days, was discharged from the North Country Community Hospital on December 21, following a spontaneous primiparous delivery with a normal primiparous postpartum course, during which time she undertook frequent leg exercises. Slight swelling of the left leg was noted by the patient two days after discharge. This became marked the following day and I was called to see her at home. Examination revealed the typical tender swelling over the left superficial femoral vein, and the left calf was two inches greater in circumference than the right, and the left thigh one and one-eighth inches greater than the right. The patient was admitted to the hospital, and Doctor Bancroft removed the clot under intravenous pentothal anesthesia. Heparin was started and continued for one week. During the first twenty-four hours this was given intravenously. The rest of the time it was given on alternate days intramuscularly. In three days the left leg had gone down one-fourth of an inch in circumference. The patient was allowed out of bed on her third day, and discharged home at the end of the week to resume the care of her baby. At this time the thigh had gone down three-eighths of an inch and the calf three-fourths of an inch. Swelling persisted for some months. The amount of swelling was somewhat dependent on the amount of activity. When the patient was seen in June, 1945, the left thigh was one inch larger in circumference than the right, the left calf was three-fourths of an inch larger in circumference than the right, and she was symptom free.

Discussion on Papers of Drs. Millen and Bancroft

DR. D. REES JENSEN (by invitation).—Thrombophlebitis or phlebothrombosis, the bland type, is a problem that besets also the general surgeon, and the question of what causes it is still unsolved. Many theories have been advanced, but none of them satisfies the conditions. Most of the patients have inflammation of the wall of the vein, and a thrombosis which is a concomitant manifestation of the disease. The question may well be asked: Why does Mrs. A. or Mr. A. get it and the next patient not get it?

I believe that, as heretofore conservative measures, such as treating this condition by elevation of the leg and long periods of rest in bed, do not satisfy the problem because it is uneconomic and the patient does not get well. In the immediate acute case treated by ligation, such as described, the result is usually excellent, and, while there are complications, they are minor in character.

We have treated a number of these cases at the New York Hospital and elsewhere which were in the acute stage, by which is meant the case occurs within a few days of surgical intervention. Conservative measures have not been satisfactory. When these patients get out of bed, they have large, swollen legs for a period of time; some of them have pain for many years; some of them eventuate into chronic ulcers; the patients must wear a support on the legs; they are never comfortable; they cannot work. I think ligation in the early case is indicated. Sulfadiazine and penicillin have been used without demonstrable benefit. There is the occasional case in which the clot breaks off in thrombectomy. That is not a criticism against the procedure for the reason that long, friable clots cannot be entirely aspirated from the external iliac and common femoral veins. It is amazing that more patients do not get them, but apparently they do not. The patient is allowed up (following thrombectomy) on the fourth, fifth, sixth, or seventh day, whereas ordinarily the patient is in bed for a long time.

I believe in giving dicoumarol on the third or fourth day following ligation. Whether that is beneficial or not I have not been able to determine.

DR. EDWARD G. WATERS.—Acute embolism that comes without warning is responsible for most of the deaths we encounter. We cannot do much about these at present; we cannot get to them quickly enough to ligate nor give the prophylactic treatment mentioned, with the possible exception of Dr. Bancroft's suggestion of thiosulfate. So we are limited to the case which gives warning, namely, the small embolism, and here we hope to prevent subsequent fatal embolism by one of the methods that we have available to us. The approach is by one of three methods which differ so much from the standard point of physiology that it is difficult to synchronize them. The first of these is a local surgical approach, the effect of which is obvious. The second is the method of blocking the preganglionic white rami communicantes of the spinal cord, thus producing dilatation, which may be achieved by spinal anesthesia, by paralumbar sympathetic block, or by high level caudal anesthesia reaching the tenth dorsal. The third is a purely medical approach by which we hope to prolong the bleeding time, check clot propagation, and prevent a fatal outcome when a small embolism has already occurred.

From different groups interested in the various approaches we get reports that are good, bad, and indifferent.

I think we have to go a long way yet before we finally get our bearings. What will the approach be to this subject ten years hence compared with that at the present time? The attitude now is to prevent the recurrence of an embolism when thrombosis is already present or preventing the extension of an endovascular thrombus.

At our clinic (Margaret Hague Maternity) we have not been using the operative approach. We have used caudal anesthesia, a great deal of sympathetic block, and more recently, dicoumarin.

I do not believe that, routinely, taking the prothrombin time in a patient with leg-calf tenderness is going to help very much. The readings are usually normal. In one recent case treated with dicoumarin for five days the prothrombin ratio dropped from 83 to 7 per cent. This may often occur, but is easily corrected by giving vitamin K and supplementing with whole blood transfusions if any hemorrhage occurs.

I would like to hear what Dr. Bancroft thinks the future approach to this particular problem may be. Admittedly, there are failures with the surgical approach. There are inadequacies in the method which blocks the sympathetic control of the peripheral vascular system, and we have not reached the end of our possibilities with anti-clotting medication.

DR. CHARLES M. McLANE.—Will Dr. Bancroft tell us what is the best treatment for the so-called fulminating type of phlebothrombosis which occurs in obstetric patients with an acute onset, rather high fever, and pain in the ankle advancing so fast that you can almost watch the pain ascend upward to the knee and thigh. Do you think such patients should be treated by ligation or should some of the medical methods be used, that is to say, whether caudal anesthesia, paravertebral block, or anticoagulins are better than ligation?

DR. RICHARD N. PIERSON.—I would ask whether oxytocics, particularly ergotrate, should be used sparingly because of their vasoconstricting effect.

I also would like to refer to the possible effects of tobacco. A patient with her first cesarean section developed a fairly severe thrombophlebitis for which she was given heparin for two weeks and recovered. She was an inveterate smoker, and the next time she became pregnant we persuaded her not to smoke, at least toward the end of her pregnancy. Her prothrombin times were normal post partum. She was out of bed on the third postpartum day and home on the eighteenth day. Five days later she phoned stating she had a pain in the leg. She started to smoke three days previously. Smoking could have been a factor in the condition.

DR. JOSHUA W. DAVIES.—As a prophylactic in the prevention of thrombophlebitis, I question the advisability of using anticoagulants in the antepartum period because of the bleeding which may occur during the third stage of labor. It is this part of labor which causes the obstetrician considerable anxiety, and to minimize the loss of blood, various oxytocics and even local anesthetics are utilized to facilitate the contraction of the uterus, which in turn lessens the amount of blood loss. After the completion of the third stage of labor, it might be of value to administer heparin or some anticoagulant in those patients who may be confined to bed for a longer period than usual, and particularly in those patients who are disinclined to early mobility.

I would like to ask Dr. Bancroft, why it is necessary to ligate the saphenous vein in addition to the ligation of the femoral vein. Ligation of the femoral vein would prevent the dislocation of the clot, but it seems to be the practice to ligate the saphenous vein also. Perhaps this procedure more effectively interrupts the sympathetic nerve supply to the superficial veins, and affords relief from pain by preventing vasospasm.

DR. BANCROFT (Closing).—I cannot answer all the questions that have been asked, but there are some interesting things in connection with a study of thrombosis and embolism. I have been working on this subject for quite a number of years. There was a time when we had a fund at the Fifth Avenue Hospital, and we did routine prothrombin and fibrinogen tests on all patients both pre- and postoperatively. I am very distinctly of the impression that there are potential "clotters" just as there are potential "bleeders." For example, we had one patient who rested her arm on a table and had a thrombosis of the median basilic vein.

The factors that we consider causes of thrombosis and embolism are trauma and infections and, most important, hemostasis. In our studies, we found that a certain number of patients have high prothrombin indices before operation, and that 14 per cent of all postoperative cases in our routine tests had high clotting factors, i.e., high prothrombin and fibrinogen. Of this 14 per cent, 2 per cent developed vascular accidents such as phlebothrombosis and thrombophlebitis. On analyzing the postoperative patients who were in the 14 per cent with high clotting factors, we found that they ran a longer elevation of temperature than is normal, and I feel confident that this group are the potential "clotters," and they may have had deep thrombosis which did not appear on the surface.

I believe that prothrombin is a very definite indicator and that it does not vary much. In other words, we have taken the normal as the denominator and the patient as the numerator, and found it was only about 0.8 per cent that puts a person in the bleeding diathesis and only 1.15 per cent that puts him in the clotting diathesis, and that it does not show a wide variation.

I believe that the high incidence of pulmonary accidents occurring in Sweden may have something to do with the high protein and fat diet prevalent there. The Smörgasbord which is featured in most Swedish restaurants has a very high fat content.

Dr. Kosmak asked about hemorrhage. I think you can get hemorrhage from any anticoagulant. There have been hemorrhages reported from the mucous membranes and from wounds following the use of dicoumarol. I think that in the last report from the Mayo Clinic, more hemorrhages have been reported from the use of dicoumarol than from heparin. With heparin, its anticoagulant action ceases within two hours after its discontinuance.

Dr. Davies asked why, if we ligate the femoral vein, do we ligate the long saphenous vein? We don't always, but there are many patients with a process in both femoral and saphenous veins. I have had three patients in whom the femoral vein was exposed and it did not contain a clot, whereas when the long saphenous vein was investigated, it was found to contain a clot which extended into the femoral vein and extended up into the iliac. So if you are looking for a clot and it is not found in the femoral vein, you must look for it in the long saphenous.

Loose abdominal dressings, early feedings, and early evacuation of the bowels are important in the prevention of distention. A tight abdominal dressing is likely to create

distention and with distention there is compression of the vena cava with resultant venostasis.

Gentle handling of tissues is another factor in the reduction of emboli.

Insofar as the element of smoking is concerned, in the patient to whom Dr. Pierson referred, it must be remembered that in her case, the arteries were also affected, and often it is not just a venous condition; it is a combination of both. She had an absent dorsalis pedis and a very small posterior tibial pulsation, and it seemed that this might not be Buerger's disease, but something similar to it. Therefore, one has to consider tobacco and the spasm of tobacco as a factor in a good many of these conditions.

Dr. Waters has referred to some serious problems. I don't think I can answer them. The inflammatory type associated with periphlebitis, as evidenced by elevation of temperature, the sore, tender, and swollen leg, will be greatly benefited by lumbar block. In a series analyzed by Gallie of Toronto, only 10 per cent of emboli occurred in this group.

As for proximal ligation, some patients with phlebothrombosis and milk legs do not "shoot emboli" and get well, and that there is a fairly large group which "shoot emboli" and sometimes they are too big to do anything about, so if one goes into the surgery of vein ligation, one has to face the fact that one will perform a number of unnecessary operations.

I have used heparin for eight to ten days and found that, two days after stopping, the patients had shot emboli.

In answer to Dr. McLane, I assume he meant what I spoke of as the high temperature of acute phlebitis, what we used to call acute phlebitis and not the silent type, where the patient shoots an embolus. There I have not found that penicillin or any drug therapy has done much good. In cases in which we have excised veins we have never been able to grow cultures; why, I do not know. I think if I had a thrombus in my own leg, I would prefer ligation of the long saphenous vein rather than blocking of the lumbar ganglia. I feel that I would be less worried about it. I have seen one or two cases of novocain poisoning that were rather terrible to behold. They tell me that if barbiturates are given before the novocain, it diminishes the toxicity of the drug, so if we were to consider the occasional one who may be susceptible to novocain and give barbiturates, it may be of value.

To Dr. Millen, I would say I believe it is not only the flexion of the knees, but also the pressure on Poupart's ligament with a patient in the Gatch bed and tight abdominal dressings which may be a factor in venostasis.

THE PSYCHOSOMATIC ASPECT OF DYSMENORRHEA*

A Sensory Conditioning Process

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DYSMENORRHEA, in 1946, ranks as a major dysfunction among women of the Occident, and also among the educated classes of Oriental women. It is still spoken of as the "riddle of the ages." In the Ayur Veda, written 1,000 years B.C., there is mention of the pain of menstruation. It was Hippocrates who recommended cervical dilation as treatment for menstrual pain.

Today's increasing prevalence of dysmenorrhea may stem from the fact that modern mechanical inventions have relieved women of much drudgery, thereby giving them more time for introspection. The dissemination of modern medical knowledge has made the public conscious that minor disorders may lead to major catastrophes. The unfortunate angle of such propaganda is that minor disorders, when analyzed by the sufferer, and if dwelt upon, can easily lead to discomforts of major proportion.

The physiologist, the neurologist, and the psychiatrist tell us that the synthesis and analysis of stimuli that come from within and from without are functions of the cerebral cortex. From this hypothesis we hope to show that:

1. Dysmenorrhea for the most part is a normal sensory conditioned process that reaches abnormal levels.
2. That multiple inadequate sensory stimuli coming from several sources—of which pain is the dominant one—are effective in reaching threshold levels.
3. That repetitive, painful monthly stimuli above the threshold level increase the sensitivity to subsequent stimulation.
4. That psychic patterns are formed in the cortex.
5. That these phantom patterns are reversible.

To demonstrate the mechanism of increased sensibility we propose to point out some of the normal physiologic changes in the menstrual cycle that become exaggerated by a process of sensory conditioning and integration, and form psychic patterns in the cerebral cortex which produce pain and other disagreeable symptoms. We hope to show that these symptoms are not products of the imagination, but have a physiologic basis.

Classification

Since dysmenorrhea is a symptom complex rather than a disease, it has been given numerous descriptive titles to fit the prevailing theories. The conception that all disease was based upon cellular pathology, as taught by Virchow, led to a fruitless search in the majority of cases of dysmenorrhea. For a time, in-

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vestigators felt that if no diseased tissue were found, it was because of incomplete examination or due to the use of a microscope not sufficiently powerful to reveal the cause.

In the main, we may classify dysmenorrhea patients in one of two types: *primary* or *functional,* in which no pathology is found to account for symptoms; and, *secondary* or *organic,* in which is present some demonstrable local pathology capable of producing the symptom.

As science discovers more about dysmenorrhea, the functional nature of the disability becomes more and more apparent until at present many authorities hold that even chronic secondary dysmenorrhea has psychogenic factors in the background. If one considers case histories where painful cyclic symptoms appear (1) in congenital absence of the uterus, and (2) persist after removal of the uterus but not the ovaries, it becomes definitely certain that not all symptoms arise from the uterus itself.

Evolution of Dysmenorrhea

Since all are familiar with the symptoms of functional dysmenorrhea, it is necessary only to review some of the contributory factors:

1. As a rule, the symptoms begin when the girl becomes sex conscious, rather suggestible, and more or less emotional.
2. There is a gradual increase in severity of the symptoms over a period of several years, the peak being reached between the ages of 18 to 20, with gradual subsidence due to normal changes of environment and interpersonal relationships.
3. Not all periods in the same individual are of the same severity. Emotional conflicts of any sort tend to exacerbate the pain, while agreeable social activities or praise from parent or employer have an opposite effect.
4. These symptoms are found in normal, healthy, ovulating girls and are usually cyclic, that is, they reappear at regular intervals.
5. Dysmenorrheics have a lowered threshold for pain, and this holds true even during the climacterium.
6. Some of the measurable physiologic changes of ovulatory menstruation are: (1) extracellular edema, (2) basal temperature changes, (3) muscle sensitivity (or tonicity), (4) vascular changes,[1] (5) breast changes, (6) emotional changes, (7) genital changes.

Symptomatology

All women who ovulate show these changes, although many deny their presence unless specifically requested to look for them. We find women who declare they have no warning of the onset of menstruation. When asked if they have pelvic discomfort, bladder frequency, engorged breasts, or a tingling feeling in the breasts, or headaches, they may or may not admit such feelings. Even if, upon direct questioning, they admit they feel tired, irritable or restless, depressed or unusually stimulated, or are conscious of fullness in the head, they insist they never let these symptoms interfere with their activities. Our patients universally admit emotional or nervous instability and one or more physical symptoms. In other words, women do have warnings of impending menstruation, if they look for and acknowledge them.

Exceptions are those females who do *not* ovulate at the beginning of the menarche, some in the reproductive cycle, and many approaching the menopause. "If she has dysmenorrhea she probably ovulates," is a precept in the medical profession. Other exceptions are cases of acute inflammation and cases where the pattern of pain has been well established.

Etiology

There are as many alleged causes as there are women who suffer from this disorder. Each dysmenorrheic has her own idea concerning the cause, but few suspect the psychosomatic origin of the dysfunction in herself. Many doctors unconsciously find pathology to fit their preconceived ideas as to causes.[2]

It is important to bear in mind that dysmenorrhea occurs mostly in normal, healthy, ovulating women with no estrogen-progesterone imbalance, and whose bleeding is cyclic or regular[3-6] and accompanied by a secretory type of endometrium.

Mechanisms Responsible for Pain Variations

The general theories regarding the mechanisms responsible for functional dysmenorrhea as we know it today are all based on some disturbance in the uterus either from:

1. Disordered myometrial contractility
2. Faulty endometrial separation or disintegration
3. Disturbance of the estrogen-progesterone balance
4. Chronic inflammation of visceral sympathetic connections.

There is no agreement among investigators that any single one of these factors is the cause of dysmenorrhea, except when pelvic inflammation is present.

It is significant that childbirth and age increase tend to accentuate the pathologic changes in the musculature, the endometrium, and the arteries and nerves of the uterus, yet dysmenorrhea, when untreated, seems to diminish as these changes become more noticeable.

What Is Pain?

Since *pain* is the aspect of the disease with which we are primarily concerned, it is necessary to understand something of the nature of pain and the mechanism by which it is raised to conscious levels. Lewis,[7] who has devoted years to the study of pain, says, "Pain cannot be defined, as it is something we *learn* from experience and *describe* by illustration." Main[8] says that the function of the sensory nerves is *to acquaint* the consciousness with the nature of the external and internal environment and regulate the autonomic processes.

Mechanism of Sensory Conditioning

Walker[9] says there are three levels at which pain may be integrated: (1) the cortex, (2) the thalamus, (3) the tectum mesencephalon. He states that normal appreciation of pain occurs in the cerebral cortex. That at this level painful stimuli are modified by the activity of other cortical centers—that

is, that perception may be *either* aggravated or inhibited. It is *aggravated* by focussing the subject's attention on exciting stimuli, which may give rise to anticipatory states of anxiety or agitation such as may be manifested when a subject faces a dental appointment. It is *inhibited* when a subject participates in games of concentration or excitement, such as boxing matches or football games—sometimes to a point where *no* pain at all is felt.

In dysmenorrhea the question naturally arises, how do the normal molimenal symptoms following ovulation become exaggerated into the disagreeable disorders of which pain is the predominant symptom?

Wolff and Goodell,[10, 11] using a series of subjects, have shown that the pain threshold (perception) can be raised approximately 30 per cent for long periods by placebos; by distraction; and by suggestion or hypnosis. The success or failure of analgesics is markedly influenced by the confidence or lack of confidence the subject has in the efficacy of the drug (Figs. 1 and 2).

Haman[12] has shown that the dysmenorrheic individual has a relatively low pain threshold and is, therefore, more sensitive to all sensory stimuli.

Sensory conditioning is a stepped-up process of perception induced by repetition. It is a normal physiologic process of learning similar to that acquired in learning to appreciate, or depreciate, various types of music. To cite some examples of sensory conditioning in experimental psychology:

TABLE I. PAIN THRESHOLD IN FOUR GROUPS OF HUMAN SUBJECTS AS MEASURED BY THE SENSIMETER

GROUP	NO. OF CASES	AVERAGE PAIN THRESHOLD MEAN OF READINGS FROM RIGHT AND LEFT THUMB (SENSIMETER UNITS)
I. Dysmenorrheic	100	12.2
(a) Primary	50	11.4
(b) Secondary	50	12.9
II. Nondysmenorrheic	100	14.9
III. Postmenopausal	100	15.2
(a) Surgical	50	15.2
1. Had dysmenorrhea	25	14.7
2. Had no dysmenorrhea	25	15.6
(b) Physiologic	50	15.3
1. Had dysmenorrhea	25	14.4
2. Had no dysmenorrhea	25	16.2
IV. Male	100	14.6
All women	300	14.1
All subjects	400	14.2

Mowrer,[13] after a prolonged series of experiments, using gradually increasing painful stimuli, found that the subject often manifested an hallucinatory perception of pain; that is, felt pain when no stimulus was applied. For instance, applying an electrode to a subject's skin up to 200 times, he then instructed the subject to break the connection when again she should feel pain. At the 201st application the subject broke the connection, indicating pain was experienced, although actually the electrode had not been activated.

Ellson[14] by associating sound with light over a period of time, found that 80 per cent of his subjects reported hearing sounds when the light was shown and no sounds made.

Howells,[15] by associating a high tone with a green light and a low tone with a red light, after some 5,000 repetitions, found that his subjects continued to see the corresponding colors when the different tones were sounded, although

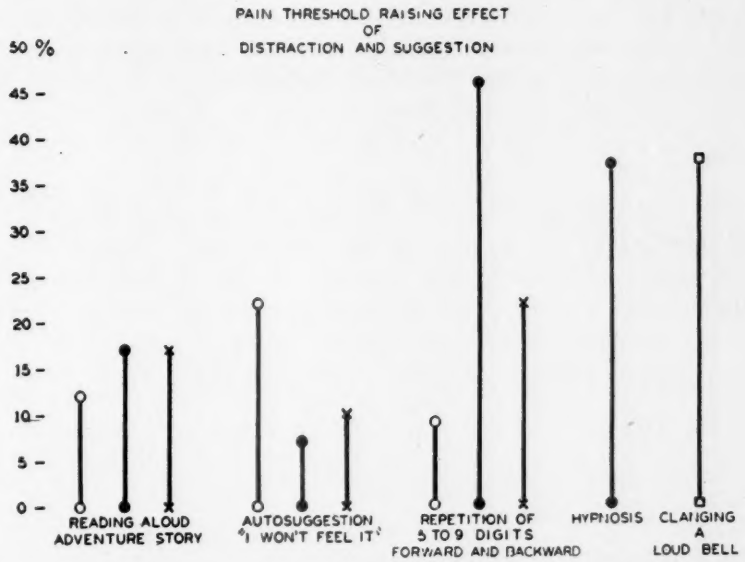

Fig. 1.—Chart showing the pain threshold raising effect of distraction and suggestion. The abscissa represents the "normal," or control threshold for three individuals; the upper circles and crosses represent their thresholds raised by the various procedures. The per cent elevation of pain threshold above the control level is represented on the ordinate. (Reproduced by permission from the *Journal for Nervous and Mental Disease*, 23: 437, 1943.)

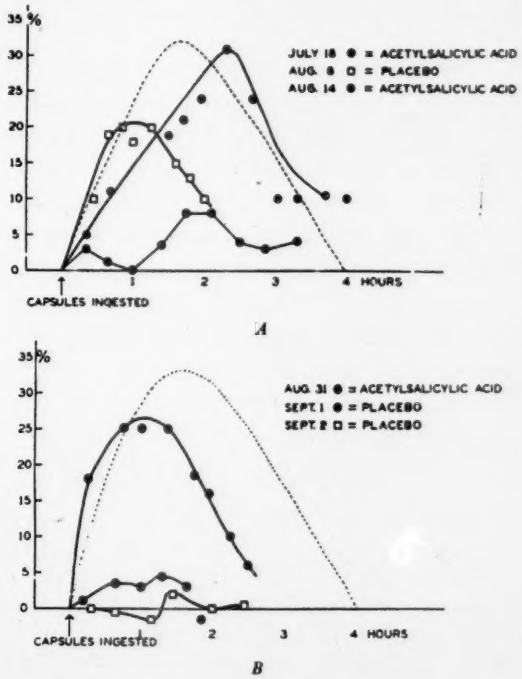

Fig. 2.—The effects of placebos and analgesics on the pain threshold of a suggestible woman. *A*, during a period of anxiety; *B*, during a period of assurance and relaxation. (Reproduced by permission from the *Journal for Nervous and Mental Disease*, 23: 439, 1943.)

the colors had been reversed. That is, the subject reported seeing the green color with the high tones, even though the red color was flashed, and vice versa.

Leuba,[16] using hypnosis to limit the subject's attention, states that "Our experiences indicate that after inadequate stimuli have been presented a number of times while the subject is experiencing certain sensations, the stimulus will of itself automatically and without intervention of any conscious process produce those sensations."

Through the demonstrations of these and many other investigators in experimental psychology we have come to believe that dysmenorrhea, the predominant symptom of which is pain, is one of the *sensory conditioning processes.*

Another, perhaps more familiar, is the intractable pain of phantom limbs, where the conditioning occurs through the repeated painful impulses arising from chronically irritated nerve endings before amputations.

Anderson and Parmenter[17] state that in animals emotional states may be induced by a feeling of uncertainty incident to the experimental procedure—a procedure involving a psychosomatic adjustment which the animal is forced to face and from which it cannot escape.

Most investigators agree that dysmenorrhea is associated with premenstrual tension which is the result of corpus luteum activity. To this we agree.

Weingraf[18] states that functional dysmenorrhea is an organ neurosis and gives the following reasons: (1) absence of pathology, (2) inconstancy of pain, (3) reversibility, (4) other neurotic stigmas, (5) amenability to a variety of treatments, (6) suppression by hypnosis.

We agree with these findings, but do not feel that the neurosis is psychodynamic as Weingraf says it is, or psychogenic as the textbooks describe it. We believe it is initiated and developed by physiologic changes rather than by suppression or repression of psychic episodes of the past. We admit that dysmenorrhea is far more common in nervous, emotional, impressionable women with inadequate personalities, but we find also that these same women have lowered pain thresholds and the condition definitely associated with corpus luteum activity.

Thus, by a normal process of sensory conditioning, a neurosis is developed and a patient's threshold for pain is further reduced.[19] We contend that the painful patterns are in the cerebral cortex. Proof of this is illustrated in the intractable pain of pelvic carcinoma that cannot be relieved by severing the visceral sympathetics, by rhizotomy, or by chordotomy.

Freeman and Watts,[20] by severing the nerve connections between the cortex and basal ganglion—lobotomy—relieve fear, anxiety, and emotional disturbances in psychopathic patients. They found that intractable pain not relieved by severing the afferent pain tracts could be relieved by *their* operation, which does not interfere with bodily activities. Van Wagenon of the Mayo Clinic by this operation has relieved the intense pain of a phantom limb after 13 preceding surgical procedures had failed. Raney[21] and White,[22] have excised the cortical tissue where the pain patterns are found and relieved the pain of phantom limb.

We feel that psychic complexes in early adolescence are not necessarily the cause of dysmenorrhea, for we find many women without dysmenorrhea who

have had harrowing experiences in childhood and whose first menstruation was accompanied by psychic shock. The suppression of pain by hypnosis is no proof that dysmenorrhea is a psychogenic process, for it will relieve the pain of childbirth (by raising the pain threshold), or the extraction of a tooth just as readily. If, by psychoanalysis, the patient can be made to believe that the cause has been removed, the pain threshold is elevated and the symptoms relieved.

We have no quarrel with present methods of treatment of dysmenorrhea so long as they produce results without exploitation of the patient. We have found through experience that some dramatic procedure performed with confidence is necessary to relieve the average patient. To tell a patient bluntly that her condition is a psychoneurosis is most likely to be interpreted by her as an insult to her intelligence. Her natural reaction will be to seek another physician who, she may feel, has a clearer understanding of her suffering.

The following are brief summaries of a few cases temporarily relieved of some, if not all, of their disagreeable symptoms:

CASE 1.—Mrs. C. J., aged 38 years, requested a panhysterectomy. All previous treatment had given no relief. She had had no preconceived complexes in regard to menstruation. However, her first menstruation was marked by premenstrual tension. After eight hours of suffering and bleeding she revealed her embarrassing condition to her mother. With each succeeding period the girl's suffering grew worse until chills, syncope, and uncontrollable nausea and vomiting accompanied all periods. The usual home remedies and surgical dilatations of the cervix were tried with indifferent success. Marriage and pregnancy gave no relief. Presacral neurectomy was performed without relief. However, a succeeding pregnancy was accompanied by several episodes of painless contractions with bleeding, and was terminated in a precipitate delivery free of pain, demonstrating the sympathetic nerves had been interrupted. This was a marked contrast to her previous deliveries. With return of menstruation, the original intense dysmenorrhea symptoms reappeared, preceded each time by a week of nervous tension and anticipation, chills, syncope, nausea and vomiting, and bed for three days.

Through partial hypnosis by Dr. Dorcus her symptoms were greatly relieved for two periods, and the patient was able to carry on her household duties for the first time. Estrogen was then given to suppress ovulation, and the next period was so relieved she came to the office to report her appreciation. The next period was preceded by a painless diagnostic curettage, and secretory endometrium was found. This period was more painful. Restriction of sodium and the administration of chloride was tried and gave some relief at the following period. At present, the patient feels greatly relieved and will seek no further help if this status can be maintained. *Result:* Partial relief by hypnosis; definite relief by suppression of ovulation.

CASE 2.—Miss A. B., aged 21 years, the daughter of a Christian Scientist, was taught by her mother the normal physiology of menstruation. She had pain with her first period, followed by periods of increasing intensity. Pentothal sodium was given to dilate the cervix. While in this suggestible stage, she was told she would be free from dysmenorrhea, but would feel the usual moliminal symptoms. *Result:* excellent.

CASE 3.—Mrs. L. C., aged 30 years, had dysmenorrhea with relief for four or five years following pregnancy. She was given sodium pentothal with feigned

dilatation of the cervix. While in this state she was impressed with the idea she would have no pain, and relief has been excellent for the past three periods. *Result:* Relief by narco-suggestion.

Numerous other patients including some with organic pathology have been relieved by hypnosis and by various injections and oral medication, accompanied by suggestion therapy.

CASE 4.—Mrs. W. O., aged 28 years, a college graduate who was known to be responsive to suggestion, was hypnotized and told that the normal symptoms associated with menstruation would be exaggerated and intensified during the following period. Definite symptoms of dymenorrhea were induced that recalled milder attacks eight years previously. *Result:* Suggestive that dysmenorrhea is the result of physiologic changes. Probably simple reinstatement.

Résumé of Spaulding's case (Virginia M. Monthly **68**: 105-107, 1941).[23]

Girl, aged 16 years, with cyclic episodes of headaches, general malaise, and severe drawing pains in both lower quadrants, but no bleeding. Uterus not felt by pelvic examination. Attempts to find and dilate the cervix were unsuccessful. Pains became more severe, necessitating confinement to bed for from one to three days. Laparotomy was decided upon. *Operative Findings:* Congenital absence of the uterus and one kidney. Normal functioning ovaries.

After operation, patient was relieved for three months, and then symptoms returned. Comment by Spaulding: "We firmly believed these pains were not of psychic origin, for the patient had pain for fifteen months before she had knowledge she was different from other girls."

Discussion

We have given no new method of treatment, but have presented what we feel is the mechanism of much of the discomfort and suffering of dysmenorrhea.

It is generally agreed that corpus luteal activity produces physical changes such as temperature shifts, intracellular edema, muscle tonicity, breast changes, and vasomotor changes that lead to premenstrual tension and emotional instability. It is these changes that give rise to pelvic discomfort, bladder irritability, intestinal disorders, headache, fatigue, backache, and emotional upsets which are known as moliminal symptoms.

Most dysmenorrheics have been shown to have lowered pain thresholds, and are more susceptible to sensory stimuli than those with normal thresholds. By a sensory conditioning process these symptoms are exaggerated and the predominant symptoms may be expressed as migraine, painful breasts, or more often pelvic pain, since menstrual bleeding focusses the attention in the pelvis.

We have relieved cases by surgical and medical means. We have relieved an equal number by placebos and by suggestion, and also by suggestion under hypnosis. We believe that one method is as satisfactory as another, except where definite pathology is present.

We are told that the pain is an esthetic sensation that reaches consciousness in the cerebral cortex where its intensity is registered.

We believe that suggestion, either consciously or unconsciously, enters into the treatment of most cases of dysmenorrhea, since the percentage of cures as reported from either scientific or unscientific sources average about the same, except by castration or presacral neurectomy.

References

1. Brewer, J. I.: Am. J. Obst. & Gynec. **36**: 597-612, 1938.
2. Novak, E.: Textbook of Gynecology, ed. 2, Baltimore, 1944, Williams & Wilkins, p. 569.
3. Fluhmann, C. F.: Endocrinology **23**: 393-397, 1938.
4. Thorn, G. W., and Emerson, K.: Ann. Int. Med. **14**: 757, 1940.
5. Greenhill, J. P., and Freed, S. C.: West. J. Surg. **49**: 318, 1941.
6. Sturgis, S. H., and Albright, F.: Endocrinology **26**: 68, 1940.
7. Lewis, T.: Pain, New York, 1942, The Macmillan Company.
8. Main, R. J.: Synopsis of Physiology, St. Louis, 1944, The C. V. Mosby Co., p. 218.
9. Walker, A. E.: Pain, A. R. N. M. D., Vol. 23, pages 63-85, Williams & Wilkins, 1943.
10. Wolff, H. G., and Goodell, H.: Pain, A. R. N. M. D., Vol. 23, p. 434, Williams & Wilkins, 1943.
11. Wolff, H. G., and Goodell, H.: Pain, A. R N. M. D., Vol. 23, p. 1, Williams & Wilkins, 1943.
12. Haman, J. O.: Am. J. Obst. & Gynec. **47**: 686-691, 1944.
13. Mowrer, O. H.: Psychoanalyt. Rev. **45**: 62-91, 1938.
14. Ellson, D. G.: J. Exper. Psychol. **28**: 1, 1941.
15. Howells, F. H.: J. Exper. Psychol. **34**: 87, 1944.
16. Leuba, C.: J. Exper. Psychol. **26**: 351, 1940.
17. Anderson, O. D., and Parmenter, R.: Exp. Psychosomatic Med., Monograph Vol. II, No. 3-4, 1941.
18. Weingraf, Fritz: Am. J. Obst. & Gynec. **48**: 475-488, 1944.
19. Gantt, H.: Pain, A. R. N. M. D., Vol. 23, pages 447-448, Williams & Wilkins, 1943.
20. Freeman, W., and Watts, J.: Psychosurgery, Springfield, Ill., 1942, Charles C Thomas, Am. J. M. Sc. **211**: 1-8, 1946.
21. Raney, R. B.: Personal communication.
22. White, J. C.: J. A. M. A. **124**: 1030, 1944.
23. Spaulding, H. C., Main, R. J., and Patterson, J. L.: Virginia M. Monthly **68**: 105-107, 1941.

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THE POSITIVE DIAGNOSIS OF HYDATIDIFORM MOLE WITHOUT EVIDENCE OF MOLE CYSTS

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MANY textbooks state that mole is positively diagnosed by the passage of mole cysts. It is true that the evidence of mole cysts alone unaided by other data is enough to make the positive diagnosis of mole. Unfortunately, however, this does not always occur, and many cases of protracted bleeding are treated conservatively in the belief that one is dealing with threatened abortion. In a recent observation I noted that only 27.7 per cent of 137 cases were diagnosed as mole. The rest were mistaken for threatened abortion, fibroma, or placenta previa.

Careful history taking and physical examination are all that is needed in making the positive diagnosis.

When the uterus is larger than the corresponding size of pregnancy, one must consider the possibility of multiple pregnancy and hydramnios. In either of these cases fetal parts are palpable and, after the fifth month of pregnancy, fetal movements are felt by the mother. When such a group of data presents itself—uterine bleeding, especially if it be of dark chocolate color; the fundus uteri is very much higher than the corresponding period of amenorrhea; no fetal parts are palpable and no history of fetal movements, though the size of the uterus is that of six or more months of pregnancy; and failure to detect the presence of amniotic fluid in the uterus—mole should be highly suspected. With regard to the character of bleeding, one must remember that chocolate colored discharge may also be present in a pregnancy with a fetus, and that red blood may also be present in mole.

Though in the majority of cases of mole the uterus is larger than the corresponding period of amenorrhea, in a few the uterus is not larger and may even be smaller than that of a normal pregnancy, and in some cases no menstruation appears after the last pregnancy so that one cannot relate the age of amenorrhea with the height of the fundus. When the condition is hydatidiform mole, vaginal examination will show that part or the whole of the lower uterine segment is full, due to its soft molar contents. Careful bimanual examination will show that no fetal parts can be appreciated.

The feeling of the fullness of the lower uterine segment as if occupied by soft tissue in conjunction with the preceding data has enabled the writer to diagnose positively the last consecutive cases of hydatidiform mole.

In mole, moreover, where the uterus is of the size of a five months' pregnancy, the uterine sound by gentle introduction into the uterine cavity reaches far beyond the lower segment. This does not happen in a normal five months' pregnancy where the sound becomes arrested by the membranes beyond the cervix. Special precaution should be observed when employing this method. It should be done with the utmost gentleness and under the greatest aseptic precautions in the delivery room or operating room where dilatation and curettage may be immediately done if necessary. For, sometimes, with the introduction of the sound, bleeding may ensue which can be stopped only by the immediate evacuation of the uterus.

I now seldom resort to this method for the history of amenorrhea and of absence of fetal movements, the fullness of part or the whole of the lower uterine

segment, in addition to the bleeding undue uterine enlargement as related to the months of amenorrhea, and absence of the fetus and of the amniotic fluid constitute the positive diagnosis of hydatidiform mole. One must rule out, of course, uterine fibroid, especially when the tumor is intramural and especially if it affects only a part of the wall including the lower segment, for such a condition gives rise also to a deep uterine cavity and bleeding. But then, in such a case the uterine cavity is empty and there is usually no amenorrhea.

The following case reports are explanatory of the method.

Case Reports

CASE 1.—P. S. L., aged 24 years, gravida ii, was admitted to the Philippine General Hospital on Sept. 30, 1944, as a case of threatened miscarriage. She had aborted at home in May, 1943, and she had had normal menstruation in July and August. Since the latter part of September and October she had scanty bleeding off and on. On admission, she had edema of the feet and legs; her blood pressure was 170/84. I was called to see the patient on October 24. The elongated pear-shaped uterus had its fundus one finger below the umbilicus. No fetal parts could be palpated, nor could amniotic fluid be detected. There was no history of fetal movements, nor could they be appreciated. Internal examination showed a small closed cervix without bleeding. But the posterior lower segment was felt to be bulging. The uterine sound could be gently introduced upward unobstructed. The diagnosis of hydatidiform mole was made and the uterus was immediately emptied of the mole cysts.

CASE 2.—L. A., aged 22 years, gravida ii, was admitted on Oct. 2, 1943, with the complaint of dark bloody discharge which had been appearing off and on since one month ago, but which had been continuous for the last fifteen days. Her first pregnancy ended in a full-term spontaneous delivery in September, 1942. She menstruated only once after delivery in December, 1942. She noticed gradual enlargement of her abdomen since June, 1943. On admission, the fundus uteri was one finger below the umbilicus. No amniotic fluid could be appreciated and no fetal parts could be felt. Internal examination showed fullness of the anterior lower segment. No resistance was met by the uterine sound introduced high up into the uterine cavity.

The positive diagnosis of hydatidiform mole was verified by the immediate curettage.

CASE 3.—P. C., 24 years of age, gravida ii, was admitted to the Philippine General Hospital on Oct. 1, 1943, as a case of threatened miscarriage. Her first pregnancy ended in a three months' abortion in May, 1943. She menstruated in June but not in July and August, and on September 29 she began to have slight bleeding. I was called to examine her on October 4, and the findings were: the uterus was enlarged as if five and one-half months pregnant, the fundus being just below the umbilicus. No fetal parts could be felt, nor could amniotic fluid be appreciated. Internally there was fullness of the posterior lower segment. The uterine sound could be introduced high up into the uterine cavity without resistance. Immediate curettage revealed small molar cysts with some admixture of placenta.

CASE 4.—C. D., aged 24 years, gravida iii, was admitted on Aug. 10, 1943, with the diagnosis of threatened miscarriage. Her first two pregnancies had ended in full-term deliveries. She complained of bleeding for the last fifteen days. The bleeding began three months and fifteen days after her last menstruation. On abdominal examination, the fundus uteri was one finger below the umbilicus, and no ballottement of fetal parts could be elicited. Internal examination showed the cervix to be closed, and there was fullness of the lower

uterine segment. She was immediately curetted, and many mole cysts of the large and fine variety, especially the latter, in addition to placenta-like tissue was evacuated.

CASE 5.—F. P., 28 years of age, gravida ii, was admitted to the Philippine General Hospital on Feb. 2, 1944, because of bleeding after three months of amenorrhea. The fundus uteri was one finger below the umbilicus, no fetal parts could be palpated, nor could amniotic fluid be detected, and there was fullness of the lower uterine segment. She was immediately curetted, and numerous fine and large mole cysts were evacuated. Early microscopy showed undue activity of the trophoblasts; but, in view of her youth and her desire for another child, she was allowed to go home with the instruction to return to the hospital in case she should bleed. She bled twice—on the thirteenth and on the twenty-fifth day after the curettage. The diagnosis of uterine chorionepithelioma by my method was made, and on Feb. 29, 1944, or twenty-six days after the curettage, a supravaginal hysterectomy and double salpingectomy were done. Section of the uterus showed button-size growth of chorioepithelioma, having a diameter of 1.5 cm. on the upper posterior wall.

Conclusion

A method of diagnosing hydatidiform mole positively is presented which consists of (1) the fullness of part or the whole lower uterine segment in conjunction with (2) undue uterine enlargement as related to the number of months of amenorrhea, (3) uterine bleeding, (4) absence of fetus as revealed by palpation auscultation and of fetal movements, and (5) absence of amniotic fluid.

CARCINOMA OF THE CERVIX DURING THE FIRST TWO DECADES OF LIFE

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THE apparent tendency of cancer to manifest itself to an increasing degree during the earlier decades[7] is a fact calling for more emphasis in current medical literature. It should be evident that no age barrier exists excluding the presence of "adult" lesions in young people.

We have been taught for so many years that cancer of the uterus always occurs about the time of the menopause, that unless one is alive to the fact that it can occur at any age, an early case in young women will be overlooked.[6]

Scheffey, Farell, and Hahn[22] note that 27 per cent of the patients with cancer of the cervix seen at the Jefferson Medical College Hospital were below 40 years of age. Hall and Bagby[7] state that 7.4 per cent of the patients with cervical cancer seen at the Barnard Free Skin and Cancer Hospital between 1933 and 1938 were below 30 years of age. Gibson[6] notes that 9.9 per cent of his series of uterine cancers were in women below 30 years. Petersen[18] states, after a review of 500 cases, that uterine cancer in general occurs in an appreciable percentage of cases between 20 and 25 years of age, 4.8 per cent of his cases occurring between 20 and 30 years of age.

Yet, despite the not infrequent occurrence of uterine cancer in young women, its presence in those below 20 years must be classed as exceedingly rare.

Koblanck[11] found only two under the age of 20 years after reviewing 6,354 cases. McGlinn[14] studied 2,291 cases and noted only 0.5 of 1 per cent under the age of 24 years. Pack and LeFevre[17] reviewed 2,134 cases of uterine cancer seen at Memorial Hospital between 1917 and 1929 and found only two within this age group. A review by Bowing and McCullough[1] of 3,000 cases of cervical cancer seen at The Mayo Clinic revealed only one below 20 years of age. Because of its rarity in these years, the diagnosis of uterine cancer is often confused or missed entirely.

Analysis of Thirty Cases Collected From the Literature

A diligent survey of the literature reveals thirty cases of true carcinoma of the cervix which occurred during the first two decades; these are listed chronologically in Table I. We are adding the thirty-first. Only those cases of histologically proved carcinoma of the cervix have been tabulated. The sarcomas and teratomas have not been included. Undoubtedly, more cases of cervical carcinoma than are listed here have occurred,[20, 23] but in those instances information was not complete enough for tabulation or the case was unavoidably missed.

TABLE I. REPORTED CASES OF CARCINOMA OF THE CERVIX IN PATIENTS 20 YEARS OF AGE AND YOUNGER

NO.	AUTHOR	YEAR	HISTOLOGY	AGE	REMARKS	5-YEAR SURVIVAL
1.	Schauta	1880	Carcinoma (malignant adenoma)	17 yrs.	Died of cancer within 7 months	No
2.	Eckardt (on Fraenkel's)	1887	Carcinoma, called sarcoma at first	19 yrs.	Probably from glands of the cervix	No
3.	Ganghofer	1888	Medullary adenocarcinoma	8 yrs.	Died of intercurrent variola	No
4.	Tschop	1897	Carcinoma, type not mentioned	19 yrs.	Believed to have been cured. No follow-up	Yes
5.	Boyd	1905	Papillary adenocarcinoma in part; other areas like endothelioma	18 yrs.	Without disease 1 year	?
6.	Philipp (on Pfaundler's)	1907	Adenocarcinoma first, then changed to endothelioma	3 yrs., 3 mos.	Passed pieces of tumor per vaginam which were adenocarcinoma on section	No
7.	Glöckner	1908	Adenocarcinoma	7 yrs.	Died of cancer, 4 years	No
8.	Bumm	1909	Adenocarcinoma	7 mos.	Died in 8 weeks. May have started in vaginal mucosa next to cervix	No
9.	DeRouville	1912	Epithelioma	18 yrs.	No recurrence 10 months after radical panhysterectomy	?
10.	Cragin	1913	Carcinoma, type not mentioned	18 yrs.	Without disease 5 months after radical panhysterectomy	?
11.	Wells	1913	Adenocarcinoma	18 yrs.	No evidence of disease, 4 years. Radical vaginal hysterectomy	?
12.	Adams	1915	Adenocarcinoma at first, then changed to teratoma	2 yrs., 6 mos.	Entire cervix and fundus were involved	No
13.	Darnall	1920	Adenocarcinoma	20 yrs.	Died postoperatively; pulmonary embolus	No
14.	Findley (on Franz's)	1924	Adenocarcinoma	6 mos.	Seen in Franz's clinic. Died of cancer in 10 days	No
15.	Aguinaga	1925	Carcinoma, type not mentioned	14 yrs.	Cautery and radium. No recurrence at 13 months	?
16.	Heusinkveld	1925	Adenocarcinoma	20 yrs.	Without disease 4½ yrs. Died of cancer 5½ years	Yes

TABLE I—CONT'D

NO.	AUTHOR	YEAR	HISTOLOGY	AGE	REMARKS	5-YEAR SURVIVAL
17.	Lisa and Cornwall	1926	Squamous carcinoma	16 yrs.	Died within 5 months	No
18.	Bonner	1927	Adenocarcinoma	13 yrs.	Without disease 19 months. Cautery removal cervix and radon seeds	?
19.	MacDonald	1929	Adenocarcinoma	10 yrs.	No follow-up	?
20.	Morse	1930	Adenocarcinoma	10 yrs.	Died of cancer, 1 year. Inoperable. May have come from fetal rests in pelvic cavity (Ewing)	No
21.	Pack and LeFevre	1930	Adenocarcinoma	20 yrs.	Probably from embryonal rests. Died of cancer 4 years	No
22.	Amesse	1932	Adenocarcinoma	24 mos.	Questionable whether origin in cervix or fundus	No
23.	Scheffey and Crawford	1932	Adenocarcinoma	22 mos.	Died of cancer in 7 weeks	No
24.	Glass	1933	Partly adenocarcinoma and partly squamous carcinoma	16 yrs.	Died of cancer, 3 years, 3 months	No
25.	Lockhart	1935	Adenocarcinoma, papillary type	2 yrs., 3 mos.	Symptoms began at age of 14 months	No
26.	Ludwig	1936	Adenocarcinoma	16 yrs.	No evidence of cancer, 5 years. D & C with cautery removal of cervix. Radium (3,160 mg. hrs.) and x-ray	Yes
27.	Bowing and McCullough	1941	Adenocarcinoma	13 yrs.	Alive and well 6 years. Cauterization of cervix with 676 mg. hrs. cervix applicator	Yes
28.	Shaw	1941	Adenocarcinoma	15 yrs.	Died within 8 months	No
29.	Morehead	1944	Squamous carcinoma	19 yrs.	Died of cancer 3 months	No
30.	Morehead	1944	Squamous carcinoma	20 yrs.	No evidence of cancer, 2 years, 4 months. Radium	
31.	Taylor and Pollack	1946	Adenocarcinoma	18 yrs.	Alive with cancer, 9 months. Inoperable. Radium and x-ray	

Bowing and McCullough[1] reviewed the literature in 1941 and found only eleven proved and classified cases of cervical carcinoma below 20 years. They added a twelfth. Morehead[15] in 1944 found seventeen cases of histologically proved cervical carcinoma in patients 20 years of age and younger.

The youngest case, 6 months old, was seen in Franz's clinic in Berlin. Findley[2] examined the specimen and made note of the extraordinary age.

It is of interest to note that the overwhelming majority of these patients had an adenocarcinoma. This type of histology seems to prevail among groups of younger patients with cervical cancer, although Pack and LeFevre[17] state that the average age of patients with adenocarcinoma of the cervix is the same as for those with epidermoid carcinoma. Petersen,[18] however, states that in his series the age group was lower in those patients with adenocarcinoma.

This form of carcinoma in itself, when found in the cervix, is a relatively rare lesion. In Pack and LeFevre's[17] series, only 0.42 per cent of all cervical cancers were of this type. Healy and Twombly[8] found 1.9 per cent in their cases, but in Petersen's[18] material, 9.1 per cent of the cervical cancers were adenocarcinomas. Of the patients listed in Table I, 22, or 70.9 per cent, had this type of histology. Only four (12.9 per cent) had squamous lesions, and four were not classified. The cancer of one patient had both squamous and glandular features.

There were only four patients in the collected series that survived five years. Of these four, the cure in one is of questionable authenticity and one died of cancer shortly after passing her fifth year following treatment. The two remaining cases are five-year cures. Both of these were treated by cautery removal of the cervix, and then radium in the form of a cervical applicator. One (Ludwig[13]) also received x-ray treatments.

Six patients were free from cancer for periods ranging from five months to twenty-eight months after treatment was instituted, but further follow-up information on these cases is not available. One case (Wells[25]) was free from cancer four years after treatment; one died three and one-fourth years after treatment; and two others died in the fourth year following therapy. With these exceptions, all died within a short period after beginning treatment or establishment of a diagnosis. Growth and spread of the lesion is very rapid, therefore it would seem that only when treatment is instituted early can any hope of cure be entertained.

Case Report

M. M., an 18-year-old, American born, unmarried woman, gravida 0, of Italian heritage, was first seen in the examining office of Memorial Hospital on June 16, 1945. She had been complaining of irregular and heavy vaginal bleeding for the previous two years. She started to menstruate at the age of 15 years, menses occurred regularly every thirty days and lasted for five days. They were not painful and appeared normal in all respects. At the age of 16 years she noted the onset of irregular vaginal bleeding. Mild spotting followed her usual menstrual flow, which spotting soon turned to the passage of large clots of blood and debris lasting four to five days at a time, and then suddenly ceasing. At times she would be free of irregular bleeding for two or three months, but it would eventually recur.

The patient consulted her local physician shortly after the onset of her irregular hemorrhages. A dilatation and curettage was immediately advised, but refused by the patient because of her virginity. She was therefore given "two injections of testosterone propionate, 0.025 Gm., about three weeks apart with no cessation of the bleeding. She was then given a prescription for 0.005 Gm. of stilbestrol which she was instructed to take every four hours until the bleeding stopped or the drug was used up." On this regime, her bleeding lessened and did stop, only to begin again within a short period. As soon as the bleeding started, she resumed taking stilbestrol. It is estimated that she took this medication, off and on, for two years.

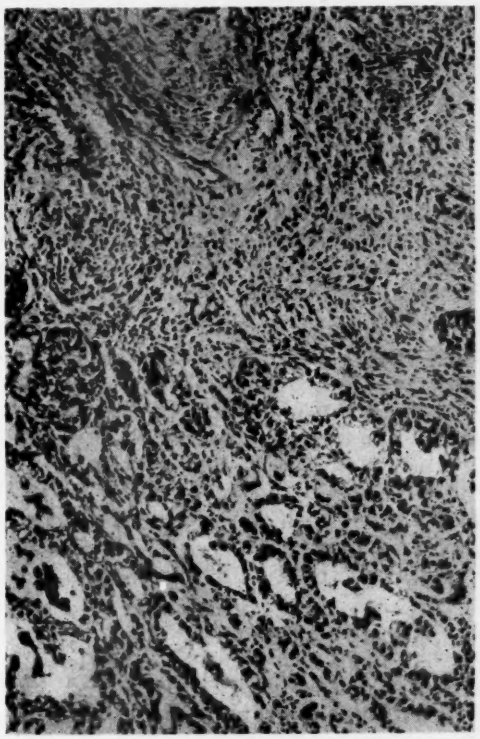

Fig. 1.—Microphotograph of biopsy taken when the patient was first examined at Memorial Hospital.

In January, 1945, the bleeding and discharge became more profuse, of longer duration, and very foul smelling. Her local physician continually advised a uterine curettage but the patient constantly refused. The bleeding became so severe by June, 1945, that a dilatation and curettage was finally permitted. Pathologic report of the curettings was adenocarcinoma, grade III, and the patient was referred to this hospital.

Physical examination was not unusual with the exception of the uterus. The fundus felt normal in size, was forward and freely movable. The adnexa were not felt. The cervix was replaced by a huge fungating tumor the full extent of which could not be made out through the nulliparous vaginal introitus. The parametria were thickened and indurated on both sides with fixation on the left. Biopsy of the tumor was taken and proved to be adenocarcinoma, grade III (Fig. 1).

Treatment was started with the million volt x-ray unit: she received 750 r. to each of six external lower abdominal ports, and then was changed to the

250 kilovolt unit where she received 1,750 r. further for a total of 2,500 r. through each portal.* Treatment was given through two ports daily, and lasted approximately six weeks, at which time the tumor was definitely movable, even in the left parametrium, and an attempt at radical panhysterectomy was decided upon. The skin reaction was moderate. On cystoscopy the bladder was normal throughout and No. 7 French ureteral catheters were passed easily to each kidney pelvis.

The patient had a laparotomy on Sept. 11, 1945. The fundus was anteverted, small, and freely movable. The adnexa were unremarkable, and there were no hypogastric nodes of significance. The parametria were invaded, especially on the left. The cervix was replaced by a large, hard, fungating mass which invaded the base of the bladder on the left side. A biopsy taken at this point during the operation was reported as "malignant tumor" on frozen section. Because of this, the case was considered inoperable and the abdomen was closed. Her postoperative course was uneventful. The wound healed well.

On Sept. 21, 1945, 3,000 milligram hours of radium in the form of a cervical applicator was inserted, and, on September 24, an additional 1,500 milligram hours was given to the cervix and parametria in the form of a vaginal bomb. She was then discharged to the outpatient department, and on October 15 received 500 milligram hours more with a small vaginal bomb.

Three months later, although she looked and felt considerably better, there was still induration and thickening in the parametria with a small crater on the left side indicative of both residual cancer and radiation necrosis. A large mass was felt in the region of both uterosacral ligaments, and probably represented more residual disease. There was marked radiation tanning of the skin of the abdomen and back. Further treatment could not be tolerated. When last seen, nine months following her initial visit to the hospital, she complained of slight bleeding from both the rectum and vagina with mild generalized abdominal cramps and urinary frequency. The mass had increased in size and was causing partial obstruction of the rectum.

Comment

The history and course of this patient are similar to other patients in the group under study. Oftentimes the first vaginal examination reveals a large, bulky tumor presenting at the cervical canal and in such a manner as to make the exact site of origin uncertain. The addition also of a foul odor with profuse bleeding, and in some cases the passage of bits of tissue, is another common feature.[16, 19, 21] Growth of the tumor and its metastases appeared to be very rapid. Gibson[6] states that unless these patients are seen within the first three months of disease, a radical operation cannot be done. The fairly quick downhill course seen in this case, despite the application of radium and x-ray to the limit of tolerance, was the usual picture in the majority of others.

It is of little advantage to speculate on the role played by the endocrine preparation given to this patient. Geist and Salmon[4] could find no evidence of abnormal proliferation in the endometrial or vaginal mucosa of 206 patients who had been treated with huge doses of estrogens over periods of time extending to five and one-half years. Nevertheless, that estrogens are possibly carcinogenic under certain circumstances and may play a role in the genesis

*The 1,000 kilovolt unit broke down and, rather than wait for its repair, treatment was immediately changed to the 250 kilovolt machine.

of uterine cancer has been the subject of much clinical and laboratory research.[3, 5, 9, 10, 12, 22, 24] Because this possibility, no matter how remote, is fraught with such serious implications, it should at all times be considered.

However, in this particular case, the exact amount of estrogens taken is unknown, and certainly, we cannot say that the patient did not have cancer at the very start of her symptoms before any medication had been taken. The important lesson to be learned is that indiscriminate use of endocrine therapy for the control of abnormal uterine bleeding often masks an underlying organic cause. Endocrine preparations of various sorts are being increasingly used to administer "cures" when the disease itself not infrequently is cancer. Because of this practice, the diagnosis of uterine cancer is often delayed. Scheffey and his co-workers[22] have recently reported a series of cases of uterine cancer referred to them in which the correct diagnosis was long withheld because of the administration of endocrine preparations, thus lulling both patient and doctor into a false sense of security and dampening the ultimate prognosis.

Summary

Thirty patients, 20 years and younger, with true carcinoma of the cervix were reviewed from the literature. A similar lesion in a young woman of 18 years was presented by us. The histologic type in 22 patients was adenocarcinoma. In the majority the clinical course was progressively downward. Four patients survived five years.

References

1. Bowing, H. H., and McCullough, J. A. L.: Am. J. Roentgenol. **45**: 819, 1941.
2. Findley, Palmer: in Abt's Pediatrics, IV, Philadelphia, 1924, W. B. Saunders Co., p. 1234.
3. Gardner, W. U., Allen, E., Smith, G. M., and Stray, L. C.: J. A. M. A. **110**: 1182, 1938.
4. Geist, S. H., and Salmon, U. J.: Am. J. Obst. & Gynec. **41**: 29, 1941.
5. Geist, S. H., Walter, R. I., and Salmon, U. J.: Am. J. Obst. & Gynec. **42**: 242, 1941.
6. Gibson, G.: Am. J. Obst. & Gynec. **1**: 273, 1920.
7. Hall, N., and Bagby, J. W.: J. A. M. A. **110**: 703, 1938.
8. Healy, W. P., and Twombly, G. H.: Am. J. Roentgenol. **49**: 519, 1943.
9. Hodgson, J. E., Dockerty, M. B., and Mussey, R. D.: Surg., Gynec. & Obst. **81**: 631, 1945.
10. Ingraham, C. B., Black, W. C., and Rutledge, E. K.: Am. J. Obst. & Gynec. **48**: 760, 1944.
11. Koblanck, R.: Veit's Handbuch der Gynaekologie, III, pt. 2, 649-805, 1908.
12. Lacassagne, A.: Compt. rend. Acad. d. sc. **195**: 630, 1932.
13. Ludwig, D. B.: Am. J. Obst. & Gynec. **31**: 536, 1936.
14. McGlinn, J. A.: New York M. J. **90**: 209, 1909.
15. Morehead, R. P.: Arch. Path. **38**: 141, 1944.
16. Morse, A. H.: Am. J. Obst. & Gynec. **19**: 520, 1930.
17. Pack, G. T., and LeFevre, R.: J. Cancer Research **14**: 167, 1930.
18. Petersen, R.: Surg., Gynec. & Obst. **29**: 544, 1919.
19. Philipp, P. W.: Ztschr. f. Krebsforch. **5**: 326, 1907.
20. Puccioni, L.: Riv. ital. di ginec. **20**: 17, 1937.
21. Schauta, Friedrich: Wien. med. Wchnschr., 1046, 1880.
22. Scheffey, L. C., Farell, D. M., and Hahn, G. A.: J. A. M. A. **127**: 76, 1945.
23. Smythe, F. W.: Am. J. Obst. & Gynec. **34**: 317, 1937.
24. Taylor, H. C., Jr.: Am. J. Obst. & Gynec. **23**: 309, 1932.
25. Wells, B. M.: Am. J. Obst. & Gynec. **67**: 145, 1913.

ACUTE LEUCEMIA AND PREGNANCY

Report of Fatal Case Treated With Penicillin

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THE relatively rare combination of pregnancy and acute myelogenous leucemia in which the effect of penicillin was studied warrants the reporting of this case.

First Admission.—M. W., a pregnant white housewife, aged 34 years, entered the medical service of the Metropolitan Hospital on March 3, 1945, with a marked sore throat and difficulty in swallowing of four days' duration. Two weeks before admission she noted headache, backache, malaise, weakness, and a temperature of 101° F. One week later she felt well enough to resume her household duties. Four days before admission the same symptoms returned and her temperature rose to 103° F. When her condition persisted unchanged after a brief course of sulfonamide therapy, the patient was taken to a private hospital where her blood picture was found to be that of an acute myelogenous leucemia. Since her condition remained critical, she was transferred to the Metropolitan Hospital where the diagnosis of acute myelogenous leucemia was confirmed.

Past history revealed that prior to the onset of her present illness on Feb. 14, 1945, she was in excellent health, except that she bruised easily. Unfortunately, no blood examination was done at any time before her present illness. Her first pregnancy ten years ago was uncomplicated, and her only child, a boy in good health, was found to have a normal blood picture. Menstrual history was essentially normal. She was five months pregnant on admission, her last menstrual period having occurred on Sept. 24, 1944.

The family history was essentially noncontributory.

On admission, her temperature was 101° F., pulse 100, and blood pressure 115/60. Physical examination revealed a moderately obese, pregnant woman who appeared markedly pale, toxic, and weak. She was in respiratory distress due to her swollen, edematous pharynx which was also painful and ulcerated. Both tonsils were enlarged and covered with mucus. On the left anterior tonsillar pillar there was a superficial ulceration, bleeding easily on touch. The gums were congested; the right side of the neck was more swollen and tender than the left. Both eyes were suffused. Examination of the ears and nose was noncontributory. There were enlarged, firm, tender cervical lymph nodes and small inguinal nodes.

Examination of the heart and lungs was negative. The breasts were enlarged. The liver and spleen were not palpable on admission nor at any subsequent time. The uterus extended to one finger below the umbilicus. Fetal movements and heart wounds were present.

The peripheral blood picture on admission was as follows: erythrocytes, 2.10 million; leucocytes, 90,000; differential count, 70 per cent myeloblasts, 10 per cent promyelocytes, 10 per cent polymorphonuclear neutrophiles, and 10 per cent lymphocytes (Fig. 1). Rare normoblasts were noted. The bone marrow examination revealed a markedly hyperplastic marrow with severe reduction of the erythroid elements (Fig. 2). There were 47 per cent myeloblasts, 28 per cent promyelocytes, 10 per cent neutrophilic myelocytes, 1 per cent metamyelo-

cytes, 3 per cent stab neutrophiles, 7 per cent segmented neutrophiles, 3 per cent lymphocytes, 1 per cent eosinophiles, rare megakaryocytes, and five normoblasts per 100 white blood cells. The granulocytes gave a positive peroxidase reaction.

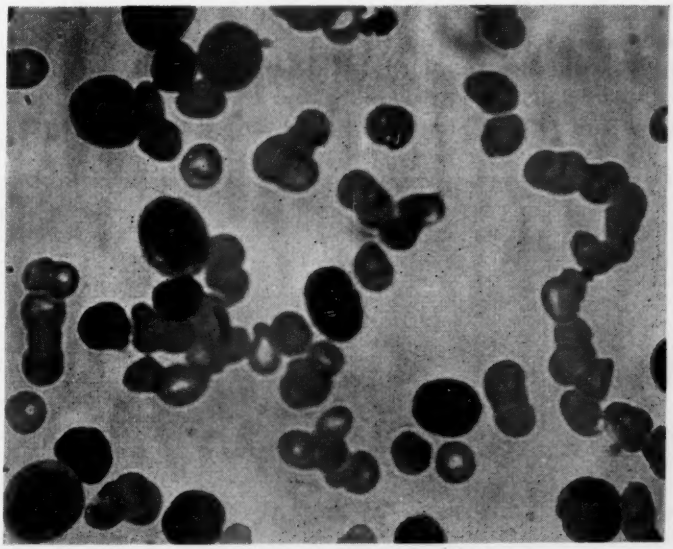

Fig. 1.—Peripheral blood smear of mother on admission showing presence of myeloblasts and promyelocytes (oil immersion).

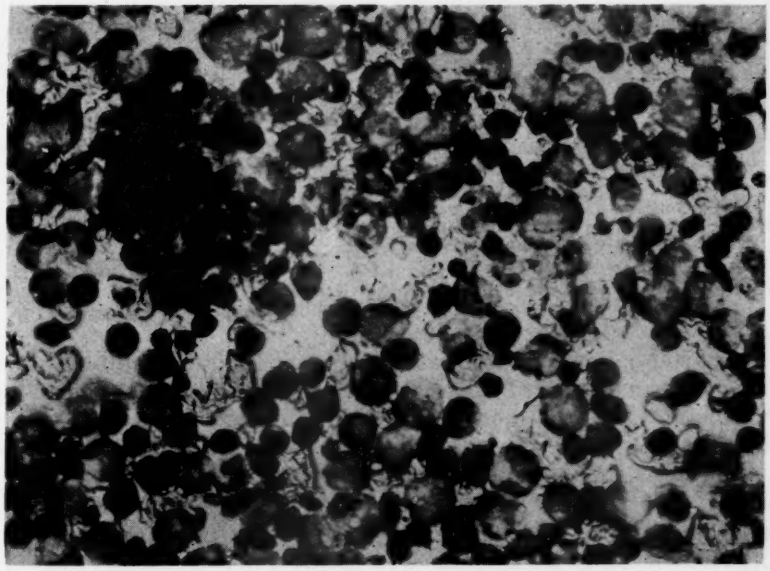

Fig. 2.—Bone marrow smear of mother showing marked cellularity as well as myeloblasts and promyelocytes (high power).

On March 6 the coagulation time as determined by the capillary glass tube method was six minutes, the clot retraction time was normal, and the bleeding time was one and one-fourth minutes. The Paul-Bunnell reaction for infectious mononucleosis was negative. The basal metabolic rate was +17, and the blood Wassermann test, as well as several blood cultures, were negative.

In view of the preceding findings, it was believed that the patient suffered from an acute myelogenous leucemia presenting throat lesions and aggravated by secondary infection. Because of this the patient received 10,000 Oxford units of penicillin intramuscularly every three hours after two initial doses of 20,000 and 15,000 units. Oxygen was given and frequent throat irrigations, as well as mouth washes with equal mixtures of hydrogen peroxide and water, were initiated. Under this therapeutic regime the clinical condition of the patient improved rapidly, and her temperature dropped to normal (Fig. 3). Despite this clinical improvement, however, her blood picture continued to show the presence of a high percentage of myeloblasts and other early forms (Table I).

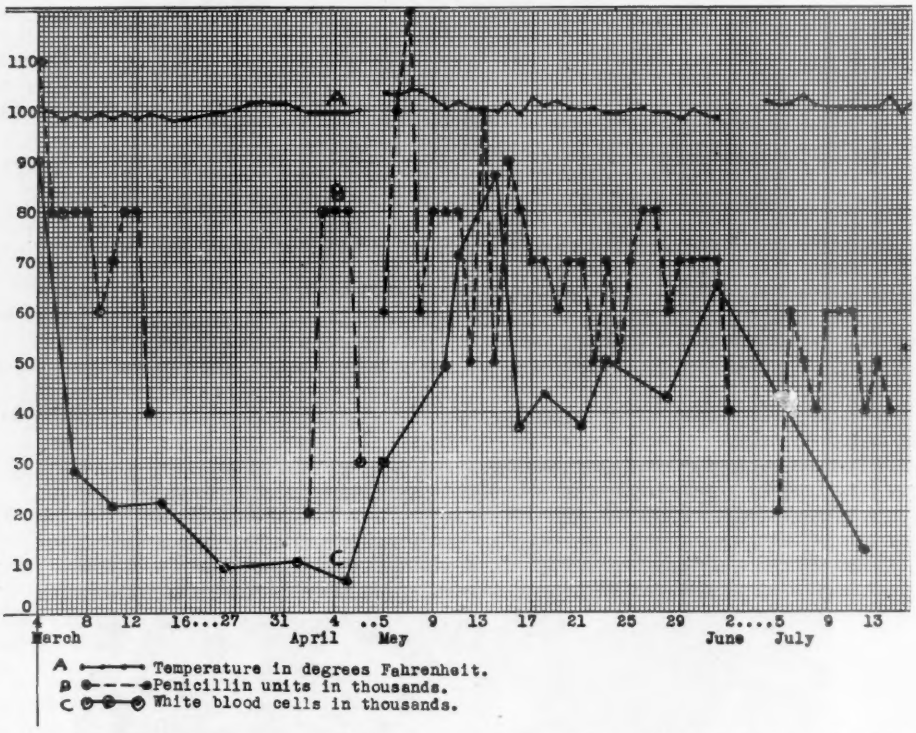

Fig. 3.—Graph demonstrating the relationship of temperature and white blood cell count to total daily penicillin dosage.

Six days after admission the patient started to stain vaginally, but had no labor pains. A transfusion of 250 c.c. of type A blood was given to relieve the patient's anemia. Half an hour after the conclusion of this transfusion the patient experienced a reaction with severe chills, rapid pulse, and a rise in temperature. The next morning the patient aborted without any postpartum complications.

Several hours after the miscarriage, an autopsy was performed on the five months' female fetus without disclosing any gross abnormalities. Histologic examination demonstrated no leucemic infiltration in the tissues, placenta, and membranes. Peripheral blood and bone marrow smears made at autopsy showed no evidence of leucemia in the stillborn.

Despite her marked anemia and abnormal blood picture, the patient continued to feel well until March 26 when she broke out into a generalized urticarial eruption for which no etiology could be determined. At this time she was receiving only iron and vitamin preparations in addition to her regular diet,

TABLE I. SUMMARY OF PERIPHERAL BLOOD AND BONE MARROW FINDINGS OF THE PATIENT DURING THE COURSE OF HER ILLNESS

DATE	HEMOGLOBIN (%)	RED BLOOD CELLS (IN MILLIONS)	WHITE BLOOD CELLS (IN THOUSANDS)	PLATELETS (IN THOUSANDS)	EOSINOPHILES	MONOCYTES	LYMPHOCYTES	SEGMENTED NEUTROPHILES	STAB NEUTROPHILES	METAMYELOCYTES	NEUTROPHILIC MYELOCYTES	PROMYELOCYTES	MYELOBLASTS
Peripheral Blood Picture													
3/ 3	55	2.2	77.4	60	–	–	10	9	4	–	3	11	63
3/ 4	55	2.2	90.0	–	–	–	10	10	–	–	–	10	70
3/ 5	–	–	–	–	–	1	13	2	4	–	12	17	51
3/ 6	–	–	–	150	–	–	–	–	–	–	–	–	–
3/ 7	56	2.3	28.5	–	–	–	–	–	–	–	–	–	–
3/ 9	–	–	–	–	–	–	19	8	6	4	12	6	45
3/10	–	–	21.4	–	–	–	–	–	–	–	–	–	–
3/12	–	–	–	–	–	–	23	17	5	2	5	5	43
3/13	–	–	–	100	–	–	–	–	–	–	–	–	–
3/14	60	2.1	22.0	–	–	–	–	–	–	–	–	–	–
3/15	–	–	–	–	–	1	36	17	7	1	8	5	25
3/16	–	–	–	–	–	2	25	23	10	3	5	5	27
3/19	–	–	16.0	–	–	–	–	–	–	–	–	–	–
3/20	56	–	12.3	–	–	–	–	–	–	–	–	–	–
3/21	–	–	11.5	–	–	–	–	–	–	–	–	–	–
3/23	–	–	–	–	1	–	43	11	3	1	5	5	31
3/24	–	–	10.9	–	–	–	–	–	–	–	–	–	–
3/26	60	2.5	8.9	–	–	–	37	27	8	–	3	2	23
4/ 1	–	–	10.1	–	–	–	–	–	–	–	–	–	–
4/ 5	–	–	6.2	–	–	–	–	–	–	–	–	–	–
4/ 6	–	–	–	–	–	–	60	14	5	1	1	2	17
5/ 5	–	2.8	30.0	–	–	–	–	–	–	–	–	–	–
5/10	–	2.8	49.0	–	–	–	–	–	–	–	–	–	–
5/11	86	2.5	71.1	70	–	–	15	6	5	2	6	14	52
5/14	80	3.0	87.2	–	–	–	–	–	–	–	–	–	–
5/16	80	2.3	37.0	–	–	–	–	–	–	–	–	–	–
5/18	53	1.9	43.5	–	–	–	13	3	7	3	9	13	52
5/21	67	2.1	37.1	–	–	–	–	–	–	–	–	–	–
5/23	73	2.6	50.3	–	–	–	–	–	–	–	–	–	–
5/24	–	–	–	–	–	–	13	13	15	7	9	6	37
5/28	50	1.7	42.9	–	–	–	–	–	–	–	–	–	–
6/ 1	53	2.5	65.2	–	–	–	–	–	–	–	–	–	–
6/19	40	2.0	21.2	–	–	–	–	–	–	–	–	–	–
6/26	53	1.7	16.0	–	–	–	–	–	–	–	–	–	–
7/12	48	2.3	12.5	–	–	–	–	–	–	–	–	–	–
Bone Marrow Picture													
3/ 4	Marked hyperplasia; rare megakaryocytes; marked reduction of erythroid elements; normoblasts 5/100 white blood cells				1	–	3	7	3	1	10	28	47
3/16	Less cellular marrow; normoblasts 15/100 white blood cells				2	–	14	18	6	3	8	17	32
7/12	Markedly hyperplastic and myeloblastic; normoblasts 6/100 white blood cells; reduced erythroid elements				1	–	5	2	2	2	3	1	84

penicillin having been stopped two weeks previously. Under symptomatic therapy the urticaria subsided.

Analysis of the patient's blood gave the following values: icteric index, 5.2; Van den Bergh, negative; cephalin flocculation test, negative; phosphorus, 4.8 mg. per 100 c.c.; alkaline phosphotase, 3.2 mg. per 100 c.c.; total cholesterol, 191 mg. per 100 c.c.; free cholesterol, 69 mg. per 100 c.c.; cholesterol esters, 122 (66 per cent) mg. per 100 c.c.; total serum protein, 5.9 Gm. per 100 c.c.; albumin, 4.2 Gm. per 100 c.c.; globulin, 1.7 Gm. per 100 c.c.; albumin-globulin ratio, 2.47. The values for blood nonprotein nitrogen, creatinine, and sugar were normal repeatedly, while the sedimentation rate was continually elevated. Urines, electrocardiograms, and roentgenograms of the chest were unremarkable.

On April 2, when the patient was afebrile, penicillin was resumed to see if it would have any effect on the blood picture. Four days later it was discontinued when the patient left the hospital in fairly good general condition with her leucemic blood picture remaining essentially unchanged save for a lower total leucocyte count (Table VII).

Second Admission.—Following her discharge, the patient remained asymptomatic for three weeks until April 30, when she developed a temperature of 101° F. and had recurrent chills. When she did not respond to sulfadiazine, she returned to the hospital on May 5 complaining of diarrhea, frequency of urination, and low back pain. Examination now revealed a pale, tired patient who still did not appear seriously ill. On her chest she had a small purpuric spot. In her left axilla was a small, moderately firm lymph node, and in her right axilla, a much smaller node. The small inguinal glands noted on previous examination were still present. Again the liver and spleen were not palpable.

During this stay in the hospital the patient did not respond dramatically to penicillin given in the usual doses, her temperature returning to normal only after four weeks. On May 7, almost two months after she aborted, the patient began to menstruate again. The Rumpel-Leede phenomenon during this admission was positive, while the blood uric acid levels were normal. On May 17 the coagulation time was five and one-half minutes, the bleeding time four and three-fourth minutes. By June 2 her clinical condition had so improved that she was able to leave the hospital.

Third Admission.—Eleven days later, however, she returned with a slight elevation of temperature, prostration, fatigue, and severe headaches. The patient now appeared to be more seriously ill and looked very tired, exhausted, and anemic. Her temperature was 100° F. Spleen and liver were still not palpable, and the lymph nodes were unchanged. Despite massive doses of iron, liver, and vitamins, the patient's condition deteriorated steadily. She developed a transfusion reaction after the second of two blood transfusions. Penicillin therapy was then resumed for one week and discontinued at the request of the patient. Under this regime no improvement in the general condition was observed, and later she complained of profound insomnia uninfluenced even by heavy sedation.

On July 11 the patient developed a right facial weakness of the peripheral type, and a day later weakness of the left side of the face with difficulty in phonation and swallowing appeared. Since the patient was lethargic and uncooperative, a complete neurologic examination could not be done. She was found to have diplopia when viewing distant objects, but no diplopia on near vision. Corneal reflexes and voluntary facial movements were absent bilaterally. A negative Rinne test without lateralization was present. Papilledema of the right optic nerve, most marked in the nasal portion, and several large recent retinal hemorrhages were noticed. The left fundus was within normal limits. Dysarthria and swallowing difficulty were present, indicating involvement

of the ninth and tenth cranial nerves. No abnormalities of the eleventh and twelfth nerves were found. Babinski responses were equivocal, and the left Achilles jerk could not be elicited.

The patient began to menstruate profusely on July 12, but following the administration of testosterone propionate her flow decreased. She became incontinent, developed a septic temperature and went rapidly downhill. On July 22, approximately twenty weeks after the patient's initial admission to the hospital, she became comatose and expired. Permission for an autopsy was refused.

Discussion

Despite the mounting number of cases reported in the literature, the combination of leucemia and pregnancy is still comparatively rare. In 1943 McGoldrick and Lapp[1] collected from the literature references to 111 cases. In only 79 was the diagnosis of leucemia associated with pregnancy well established enough for analysis. To this total they added their own case of chronic myelogenous leucemia and pregnancy. In the same year Moloney and his associates[2] reported a similar case, while van der Sar and Hartz[3] described a patient with subacute leucemia and pregnancy. During 1944, three cases of chronic myelogenous leucemia and pregnancy were recorded, two by Hochman[4] and one by Angelucci.[5] In the same year Appelbaum[6] reported a case of a pregnant woman with acute myeloid leucemia. Including the present account, the total reported number of unquestionable cases of leucemia associated with pregnancy is, therefore, 87.

The exact onset of the disease in this patient cannot be determined, since no blood studies were done before the beginning of the patient's illness, but it was felt that her leucemia apparently had begun during her second pregnancy. In favor of this view was the fact that she had carried on an active life with vigorous athletic activities up to the time of conception, and had considered herself healthy prior to the sudden onset of her symptoms. The myeloblastic picture of the peripheral blood and of the bone marrow, the marked prostration, and the throat lesions, together with the absence of noticeable lymphadenopathy, likewise indicate an acute leucemic process. The absence of a palpable liver and spleen and the progressively downward course of the patient with death in five months seem to confirm the diagnosis of acute myelogenous leucemia.

This case demonstrates the importance of doing complete blood counts early in pregnancy. Grier and Richter,[7] as well as McGoldrick and Lapp[1] state that acute leucemia is usually discovered during the fifth to seventh month of gestation, as occurred in this patient. Since in sepsis a marked shift to the left in the blood takes place and the blood picture may be indistinguishable from that found in leucemia, a leucemoid blood reaction due to sepsis, infectious mononucleosis, or drugs was ruled out in this case before the definite diagnosis of acute myelogenous leucemia was made.

Deserving of comment is the rather long course of the acute leucemia in this patient. In a clinico-pathologic study of 40 cases of acute leucemia, Kaufmann and Lowenstein[8] found the average life expectancy was 10.2 weeks, while McGoldrick and Lapp[1] estimated it to be 10 weeks after the discovery of leucemia. The patient described in this report lived about 20 weeks after her leucemia had been discovered. It is possible that the patient would have lived as long without penicillin, but it is felt that the administration of penicillin may have played a role in prolonging her life.

More than 3,500,000 units of penicillin were administered to the patient during the course of her illness. On penicillin therapy her leucocyte count declined steadily from 90,000 to 6,200 during her first admission (Fig. 3). Subsequently, penicillin apparently failed to create any great change in the blood

picture or in the fatal evolution of the disease. Our experience with penicillin confirms the reports in the literature by Herrell[9] and Keefer[10] concerning the ineffectiveness of penicillin in leucemia. It was felt, however, that the penicillin was of help possibly in controlling the superimposed intercurrent infections of the patient. Since no references concerning the effect of penicillin in acute leucemia complicated by pregnancy could be found, it is believed that this is the first such case reported.

The development of nervous system and ocular lesions during the downward course of the disease in this case was not totally unexpected. Stodtmeister and Weicker,[11] analyzing 300 cases of leucemia from the literature, found that the nervous system was involved much more frequently in leucemia than was generally assumed. Hemorrhages, infiltrations, and degenerative processes were responsible for the leucemic changes in the nervous system.

In one series of cases Hudson[12] found eye ground changes in about one-third to one-fourth of patients with leucemia. The most commonly reported fundal changes were retinal hemorrhages (as occurred in this patient) and distended veins. The cause of the papilledema in this case could not be verified post mortem, but the suspected cause was hemorrhagic involvement of the sheath of the right optic nerve with resulting impairment of the venous outflow.

The effect of pregnancy and leucemia on each other, although still not definitely determined, deserves comment inasmuch as it affects therapy and the management of such cases. Considering the effect of pregnancy on leucemia, Grier and Richter[7] note that there is usually an exacerbation of symptoms of leucemia during pregnancy and a remission after delivery, while Moloney and his associates,[2] as well as McGoldrick and Lapp,[1] believe that the course of leucemia is not greatly affected by pregnancy. In this case it was felt that the pregnancy had no great effect on the leucemia, which continued to progress even after the pregnancy was terminated.

Frequently an acute exacerbation of the leucemic process has been noted after parturition, the leucocyte count showing rapid increase in the number of immature cells. In this case the leucocyte count declined immediately after the premature labor, only to increase subsequently (Fig. 3).

On the other hand, the effect of leucemia on pregnancy is more clear-cut. Leucemia appears to predispose toward the spontaneous induction of premature labor. McGoldrick and Lapp[1] observe that, of 49 cases of acute and chronic leucemia allowed to progress in their pregnancies without interference, 21 (42.8 per cent) developed premature labor. The negative fetal blood findings and the histologic study of the fetal tissues confirm the general impression that leucemia is not found at birth in children born of leucemic mothers.

The management of pregnancy in a leucemic woman is still an unsettled problem. Forkner[13] comments that no rule can be made to apply to the management of cases of pregnancy complicated by leucemia, but that thorough consideration of all aspects of the problem in each case by the internist, as well as by the obstetrician, will lead to the best solution. Grier and Richter[7] recommend that any woman with leucemia should be advised against pregnancy.

If the pregnancy complicated by leucemia is diagnosed early, Erf and Fine[14] note that abortion is preferable. If, however, the pregnancy is well advanced, conflicting opinions result. Some believe the pregnancy should be interrupted because the treatment necessary to control the leucemia may injure the fetus. In his review of the harmful effects of irradiation, Rolleston pointed out that of 75 infants born of nonleucemic mothers who had been irradiated during pregnancy, 38 were not healthy, and 18 were microcephalic idiots.

Grier and Richter[7] feel that pregnancy should not be terminated since interference only tends to produce premature or nonviable babies and shortens the mother's life. Premature induction of labor or cesarean section is justifiable

only when the pregnancy is near term. In the case under discussion, conservative therapy was used but, as usually occurs in these cases, the patient aborted spontaneously.

For the treatment of the leucemia itself, radiation and arsenic are the two best therapeutic agents at present. The use of x-ray irradiation therapy is limited to patients with the chronic forms of leucemia. But, even here, x-ray therapy should be used cautiously, since it cannot be given without danger to the fetus. The use of radioactive phosphorus, as described by Warren,[16] may in the future prove to be a safe means of internal radiation in this condition. However, at present, arsenic in some form is recommended to produce a temporary remission in chronic myeloid leucemia without injuring the fetus.

In acute leucemia no known form of treatment is of lasting value. Frequent blood transfusions may control the hemorrhagic tendency and prolong life for a short time. Many workers feel that treatment with arsenic or irradiation is contraindicated. From the experience with penicillin in this case, it is recommended that penicillin be tried in patients with leucemia showing signs of infection and sepsis.

Summary and Conclusion

1. A fatal case of acute myelogenous leucemia and pregnancy treated with penicillin is reported.

2. Penicillin appeared to be of some value in combating superimposed infection, but did not materially improve the leucemic blood picture.

3. At necropsy no sign of leucemia was found in the stillborn fetus.

4. The treatment of leucemia complicated by pregnancy is still unsatisfactory.

References

1. McGoldrick, J. L., and Lapp, W. A.: Am. J. Obst. & Gynec. **46**: 711, 1943.
2. Moloney, W. C., Hefferman, R. J., and Kesdon, S. C.: J. A. M. A. **122**: 1170, 1943.
3. Van der Sar, A., and Hartz, P. H.: Rev. Policlin. Caracas **12**: 325, 1943.
4. Hochman, A.: J. Obst. & Gynaec., Brit. Emp. **51**: 231, 1944.
5. Angelucci, H. M.: Am. J. Obst. & Gynec. **48**: 125, 1944.
6. Appelbaum, H. S.: Ohio State M. J. 40: 536, 1944.
7. Grier, R. M., and Richter, H. A.: Am. J. Obst. & Gynec. **37**: 412, 1939.
8. Kaufmann, J., and Lowenstein, L.: Ann. Int. Med. **14**: 903, 1940.
9. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, 1943, W. B. Saunders Co., p. 129.
10. Keefer, C. S.: Am. J. M. Sc. **210**: 147, 1945.
11. Stodmeister, R., and Weicker, H.: Med. Klin. **39**: 551, 1943.
12. Hudson, A. C.: Royal London Ophth. Hosp. Rep. **18**: 153, 1911.
13. Forkner, G. E.: Leukemia and Allied Disorders, New York, 1938, Macmillan Company, p. 150.
14. Erf, L. A., and Fine, A.: Am. J. M. Sc. **195**: 8-17, 1938.
15. Rolleston, H.: Quart. J. Med. **24**: 101, 1930.
16. Warren, Shields: Am. J. M. Sc. **209**: 701, 1945.

ENDOCRINE INFLUENCES UPON THE BLOOD PRESSURE OF NORMAL AND HYPERTENSIVE RATS*

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THE fall of blood pressure during pregnancy in hypertensive rats has been described in a previous communication.[1] This observation, originally made on dogs by Goldblatt, Kahn, and Hanzal,[2] has been amply confirmed on rats,[3, 4] dogs,[5, 6] and rabbits,[7] but the cause for this decline is not known. The behavior of such hypertensive animals differs from that of hypertensive women, who usually show a further rise of blood pressure in late pregnancy. The present report is concerned with the possibility that the fall of blood pressure in hypertensive rats during pregnancy is due to an altered endocrine state.

In order to study the influence of any factor upon an animal's blood pressure, spontaneous fluctuations or those due to inherent errors of observation must be well understood. Normal adult rats show a remarkably stable blood pressure from day to day, increasing only slightly with age. The mean systolic tail pressures of 21 normal female rats of the same age and weight as those utilized in the present study has been shown to be 104 mm. Hg., with a standard deviation of 5.[1] Relatively small variations in the mean blood pressure of a group of *normal* rats are often meaningful, as in the case of normal pregnancy illustrated below.

The clinical course of experimental hypertension in the rat, on the other hand, is frequently characterized by a labile blood pressure and occasionally by spontaneous remissions or exacerbations. The more severe the hypertension, the greater is the lability. Only one of four or five hypertensive rats was found to be suitable for the type of study reported below, for we selected only those animals demonstrating less than a 10 per cent variation from the mean blood pressure in any period of two weeks prior to the start of injections.

Foa, Foa, and Peet[4] stated that there was no change in the blood pressure during pregnancy in six normal rats, but apart from this there is very little known about the effects of pregnancy, lactation, or the estrus cycle upon the blood pressures of normal rats. We have made these observations as a prerequisite to the study of endocrine influences in hypertensive rats. We then attempted to duplicate certain endocrine changes which might be related to pregnancy by the injection of hormones or the induction of pseudopregnancy in groups of hypertensive rats.

Experimental

Methods.—In all cases, hypertension was induced by a partial constriction of the left renal artery by means of a silk tie.[8] Systolic blood pressures were

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measured with a tail plethysmograph[9] on warmed unanesthetized rats, using a blood pressure cuff 25 mm. in length.*

Estrus Cycles.—In 10 normal females, four to six months of age, blood pressures and vaginal smears were taken for thirteen consecutive days. The results are given in Table I, and show a remarkable constancy of blood pressure in all stages of the estrus cycle.

TABLE I. TEN NORMAL FEMALES FOLLOWED DAILY FOR THIRTEEN CONSECUTIVE DAYS

STAGE OF CYCLE	I	II	III	IV	V
Number of readings	18	17	12	7	73
Mean blood pressure	106	104	104	103	105

Ten moderately hypertensive females of the same age were studied similarly. Since the level of hypertension varied from 136 mm. to 170 mm. in the various animals, and since not all stages of the estrus cycle were observed in every rat, the calculations are based upon variations from the mean for each animal. The sum of these variations in any one phase of the estrus cycle was then added to or subtracted from the median blood pressure for the entire group (152 mm.). It may be seen from Table II that there is no significant influence of the ovarian cycle upon the level of hypertension.

TABLE II. TEN HYPERTENSIVE FEMALES FOLLOWED DAILY FOR THIRTEEN CONSECUTIVE DAYS

STAGE OF CYCLE	I	II	III	IV	V
Number of readings	16	12	8	7	83
Mean blood pressure (see text)	153	154	150	150	151

Pregnancy and Lactation.—The blood pressure was observed twice weekly on 23 normal female rats from the day of conception to the time of weaning their litters six weeks later. In every rat there was a slight decline during the last quarter (five days) of pregnancy (Table III-A). The drop of 5.5 mm. at the end of pregnancy is 5 times the standard error of the difference between the mean blood pressure for the first sixteen days of pregnancy and the mean for the last six days, and may be considered significant (Table III-B).

During lactation there was a progressive rise of similar magnitude as shown in Table III-C, and after weaning the pressure returned to a lower level. That it did not return to the exact original level may perhaps be attributed to the increased age and size of the animals at the conclusion of the experiment. Rises of blood pressure have also been observed in hypertensive rats during the lactation period.

Pseudopregnancy.—The induction of a pseudopregnant state in hypertensive rats is difficult because of the frequent loss of estrus cycles in such animals. By inducing estrus with small doses of pregnant mare serum, however, and then stimulating the cervix uteri with a faradic current, a pseudopregnant state was induced in 11 hypertensive rats. Lactogenic hormone (prepared and given to us by Dr. W. R. Lyons[12]) caused a cessation of estrus cycles—like

*The accuracy of the measurement of blood pressure in the rat by a tail plethysmograph has been questioned recently.[10] We have checked the pressor responses resulting from the injection of drugs by both the indirect tail plethysmograph and by direct cannulation of the carotid artery, using a small Herthle manometer. The tail pressures are lower than the carotid pressures, but the rises produced by a given dosage of a pressor substance appear to be the same when recorded by either method. The fact that the tail pressure is lower than the absolute pressure should not affect the validity of the results. It has been claimed[11] that in some circumstances the warming of rats results in a rise of blood pressure. Our animals were exposed for ten minutes to a temperature of 40° C. in a thermostatically controlled ventilated box and then placed in open screen holders in an environment of 37° C. during the measurement of blood pressure.

TABLE III-A. TWENTY-THREE NORMAL FEMALES FOLLOWED THROUGH PREGNANCY

DAY OF PREGNANCY	1-4	5-8	9-12	13-16	17-20	20+
Number of readings	27	33	24	23	26	15
Mean blood pressure	105.0	105.5	104.3	106.5	100.5	98.5
Standard deviation	6.0	5.8	6.7	5.8	6.9	5.3

TABLE III-B. SIGNIFICANCE OF BLOOD PRESSURE DECLINE IN LATE PREGNANCY

DAYS OF PREGNANCY	1-16	17-22
Number of readings	107	41
Mean blood pressure and standard error	105.2 ± 0.6	99.7 ± 0.9
Standard deviation	6.1	6.1
Difference between means = 5.5 ± standard error of 1.1		

TABLE III-C. SAME GROUP OF TWENTY-THREE RATS OBSERVED DURING LACTATION

DAY OF LACTATION	1-4	5-8	9-12	13-16	17-20	21-23	WEANED
Number of readings	17	25	24	14	18	14	24
Mean blood pressure	106	107	109	115	116	113	110
Standard deviation	7.1	6.2	5.2	5.5	6.0	8.0	5.5

that seen in the pseudopregnant state[13]—in all of five additional rats. No characteristic alteration of blood pressure followed, unlike the observations noted previously when deciduomas were produced.[1] The results are placed for convenience in columns 9 and 11 of Table IV.

Control Injections and Criteria for Blood Pressure Changes.—In dealing with small groups of *hypertensive* animals, a slight rise or fall of blood pressure in less than half of the group is of little significance, and will occur frequently by chance. This is illustrated in the first two columns of Table IV, in which a group of 10 hypertensive rats received 1.0 c.c. of physiologic saline daily for

TABLE IV. THE EFFECT OF HORMONES AND OF PSEUDOPREGNANCY UPON THE BLOOD PRESSURE OF HYPERTENSIVE RATS

GROUP	HORMONE	NO.	DOSAGE	HOW OFTEN	INJECTION PERIOD (DAYS)	RANGE OF MEAN BLOOD PRESSURE	MEAN BLOOD PRESSURE FOR GROUP	EFFECT ON BLOOD PRESSURE (SEE TEXT)		
								DECREASE	NO CHANGE	INCREASE
1	Normal saline	10	1 c.c.	Daily	10	140-210	168	2	7	1
2	Olive oil	10	0.25 c.c.	Daily	10	142-198	170	2	6	2
3	Estrone in oil	5	0.05 mg.	Two days	16	150-216	164	1	4	0
4	Progesterone in oil	5	0.5 mg.	Two days	16	151-222	174	1	3	1
5	Progesterone + estradiol	6	3 mg. +0.005	Daily	10	149-218	171	1	5	0
6	Same plus silk threads	5	Same	Daily	10	150-163	156	0	5	0
7	Anhydro-hydroxy-progesterone	6	10 mg.	Daily	10	153-214	180	2	4	0
8	Chorionic hormone	7	500 Rat Units	Daily	10	137-213	173	1	5	1
9	Lactogenic hormone	5	1.0 mg.	Daily	14	140-158	148	0	5	0
10	Pregnant mare serum	8	10 Rat Units	Daily	10	143-190	162	0	7	1
11	Pseudopregnancy	11	Faradic stimulus to cervix during estrus (see text)			137-194	163	2	7	2

ten days. One rat showed a rise and two a fall in mean blood pressure. Subsequently this same group was injected with 0.25 c.c. of olive oil daily, and with similar results. By "decrease" or "increase" we mean that the average blood pressure during the injection period showed a change amounting to at least 10 per cent of the preinjection level.

The Effects of Hormones.—Selected groups of five to eight female rats weighing between 180 and 250 Gm. and having stable hypertension were given various hormones either daily (in aqueous solution) or every other day (dissolved in oil). The injection periods varied from ten to sixteen days, and blood pressure was determined every forty-eight hours. The amounts of estrone and progesterone are as large as those required for the maintenance of pregnancy after removal of the pituitary and ovaries,[14] and the ratio of estradiol to progesterone (column 3) is that which was found to be optimal for maintenance of deciduomas in the oophorectomized animal.[15]

An attempt was made to produce deciduomas by giving both estradiol and progesterone and placing silk threads in the uterus. Symmetrical enlargements of the uterus were noted a week later, but histologic examination did not reveal true placentomas and no fall of blood pressure was observed.

The anhydro-hydroxy-progesterone was administered orally by grinding the tablets with a small meal and waiting until this was consumed before further feeding. Estrone, progesterone, chorionic hormone, and pregnant mare serum were administered as indicated in Table IV. In not one of these groups was there any consistent change in the level of the blood pressure, nor any alteration in the subsequent course of the hypertension. The results are tabulated in columns 3 to 10 of Table IV.

Discussion

As will be pointed out later,[16] it is the placenta and not the fetus of the rat which is responsible for the decline of hypertension in late pregnancy. Considering the results obtained in this study, it is unlikely that the endocrine changes resulting from the presence of the rat's placenta can be held responsible for the phenomenon. The hormones were administered over a period equal to or exceeding half that of pregnancy and in amounts presumably larger than those normally existent in the pregnant rat. A variety of hormones, singly and in combination, were utilized; so that a similar pronounced fall of blood pressure should have resulted in at least one of the groups if the endocrine changes of late pregnancy were solely responsible for the effect. Furthermore, if the latter were true, the estrus cycles or the pseudopregnant state should have affected the level of hypertension as well. While there are, no doubt, several possibilities, it seems likely that either the hemodynamic effect of the placental circulation or the elaboration of a hypotensive substance by the placenta accounts for the fall which actually occurs to a slight degree in normal rats, but to a marked degree in rats with experimental renal hypertension. We did not observe any rises of blood pressure from estrogens, such as those reported in normotensive rats by Grollman, Harrison, and Williams,[17] and Leathem and Drill.[18]

Summary

In both normal and hypertensive rats the blood pressure is unaffected by the estrus cycles. In normal rats pregnancy results in a small but significant

decline of blood pressure toward the end of gestation, with a rise during lactation. These changes, though relatively slight, are qualitatively similar to the more marked fall which occurs in the hypertensive rat during pregnancy. The pseudopregnant state did not result in a decline of hypertension.

Estrone and progesterone (singly and in combination), anhydro-hydroxyprogesterone, pregnant mare serum, and chorionic and lactogenic hormones were administered in relatively large doses over a period of ten to sixteen days, and did not differ in their effects on hypertensive rats from injections of normal saline or olive oil.

The results do not justify the assumption that endocrine influences alone are responsible for the decline of blood pressure observed during late pregnancy in animals with experimental renal hypertension.

We wish to acknowledge the technical assistance of Mr. Lewis T. Brown and Mrs. Barbara Smith.

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References

1. Page, E. W., Patton, H. S., and Ogden, E.: Am. J. Obst. & Gynec. **41**: 53, 1941.
2. Goldblatt, H., Kahn, J. R., and Hanzal, R. F.: J. Exper. Med. **69**: 649, 1939.
3. Harrison, T. R., Grollman, A., and Williams, J. R., Jr.: Am. J. Physiol. **128**: 716, 1940.
4. Foa, P. P., Foa, N. L., and Peet, M. M.: Am. J. Med. Sci. **204**: 350, 1942.
5. Dawson, J. R., Jr., Cressman, R. D., and Blalock, A.: Am. J. Path. **17**: 31, 1941.
6. Rodbard, S., and Katz, L. N.: Am. J. Obst. & Gynec. **47**: 753, 1944.
7. Corbit, J. D., Jr.: Am. J. Med. Sci. **201**: 876, 1941.
8. Wilson, C., and Byrom, F. B.: Lancet **1**: 136, 1939.
9. Williams, J. R., Jr., Harrison, T. R., and Grollman, A.: J. Clin. Investigation **18**: 373, 1939.
10. Shuler, R. H., Kupperman, H. S., and Hamilton, W. F.: Am. J. Physiol. **141**: 625, 1944.
11. Proskauer, G. G., Neumann, C., and Graef, I.: Am. J. Physiol. **143**: 290, 1945.
12. Lyons, W. R.: Proc. Soc. Exper. Biol. & Med. **35**: 645, 1937.
13. Lahr, E. L., and Riddle, O.: Proc. Soc. Exper. Biol. & Med. **34**: 880, 1936.
14. Lyons, W. R.: Proc. Soc. Exper. Biol. & Med. **54**: 65, 1943.
15. Rothchild, I., Meyer, R. K., and Spielman, M. A.: Am. J. Physiol. **128**: 213, 1940.
16. Page, E. W.: Am. J. Obst. & Gynec. (To be published in a later issue.)
17. Grollman, A., Harrison, T. R., and Williams, J. R., Jr.: J. Pharm. Exper. Ther. **69**: 149, 1940.
18. Leathem, J. H., and Drill, V. A.: Am. J. Physiol. **139**: 17, 1943.

Department of Book Reviews

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Review of New Books

Gynecology

Te Linde's **Operative Gynecology**[1] is a very personal book based on his own experience and the practice of Johns Hopkins Hospital. The book is a special book for those who want to practice gynecology, and especially designed for those who had a good preliminary training as hospital residents. The author justly demands a great deal for the gynecologist to be, really six requisites—he should be an expert abdominal surgeon; should know at least the fundamentals of obstetrics; should be competent to investigate female urologic conditions; should have a broad understanding of endocrinology; should be grounded in gynecologic pathology; and finally, should be competent to handle at least minor psychiatric problems. I fully agree with these minima, but wonder how many of the Diplomates of the Board of Gynecology and Obstetrics can qualify in all of these directions.

The introductory chapters dealing with preparation, anesthesia, etc., are fully adequate, and require no particular discussion. On the whole, his attitude is very conservative. I would register some protest to the use of a midline incision, except in real emergencies such as ruptured ectopic or a patient in poor condition. However, the record as to eviscerations is good; in 5,955 laparotomies, 6 eviscerations, 0.1 per cent. Incidentally, of interest is that all of these occurred in Negro women. The death rate for evisceration is high, two out of six.

The author takes the fully justified stand that much useless surgery for retroversion and retroflexion is being done. In the rare cases where operation is indicated, he uses a modified Gilliam procedure, and where, because of other complications, particularly adnexal disease, a suspension may be considered, he uses the Coffey technique. The chapter on prolapse of the uterus is detailed. A more extensive presentation of the anatomy might have proved of value. The first operation considered is the Manchester technique, of which Te Linde says that he has never used it for complete prolapse "because it scarcely seems logical that a simple anterior colporrhaphy, with suturing of the cardinal ligaments in front of the cervix coupled with cervical amputation and posterior colporrhaphy, can support the completely prolapsed uterus." From this I gather very decisively that the Manchester operation, as practiced at Johns Hopkins, in no way conforms to the Manchester operation which I and many others perform. This is borne out by his Fig. 55, which shows incomplete exposure of the lateral parametria, bringing forward what appears to be merely a fascial sling in front of the cervix and suturing, which does not involve any parametrial structures. In fact, the exposure which I and others practice would have been much better shown by his Fig. 57*G'*, in which the base of the broad ligaments are really exposed. Therefore, what he has to say about the Manchester certainly does not apply to the extended one with which many are familiar, and statistics of which, covering more than 1,000 cases (to be published by others) show a very good record. With what the author says about vaginal hysterectomy, I am in full accord, in that 30 per cent may be expected to show poor anatomic result; also that this operation should be restricted to cases in which there is uterine disease is absolutely true. I personally have seen too many cases of prolapse of the vault in which nothing but colpocleisis promised any effective relief. Te Linde gives a very fully detailed and interesting description of the

[1]**Operative Gynecology.** By Richard W. Te Linde, M.D., Professor of Gynecology, Johns Hopkins University, and Chief Gynecologist, Johns Hopkins Hospital. With 309 illustrations in black and white, and 15 subjects in full color on 9 plates. 751 pages. J. B. Lippincott Company, Philadelphia. 1946.

Spalding-Richardson operation, a vaginal plastic in which the isthmic portion of the uterus alone is retained and utilized with its broad ligament and uterosacral attachments. He presents a record of 150 cases with no mortality and good results. This operation, of course, is more prolonged and more extensive than either the Manchester or vaginal hysterectomy.

In ascribing vaginal fixation to Brady, the author is rather careless in his bibliography. Many years previously, Fraenkel fully described the principles of this operation. Cystocele and incontinence of urine are very well dealt with, including well-illustrated Goebell-Stoeckel fascial suspension and various modifications. The description of the cure for vesicovaginal fistula is very adequate, and there is also a full description of the transplantation of ureters into the sigmoid where fistulae cannot be closed, as, for example, those following radiation of carcinomas of the bladder or vagina. The author prefers the Coffey and Jewett methods of transplantation. The technique of closure of minute fistulae by fulguration is omitted. The repair of complete tears of the perineum and of rectovaginal fistulae is described, but here, as in several other places, it appears to me that too many sutures are used, or at least indicated in the illustrations, as for example Fig. 106. I can agree with the statement that 50 per cent of the hemorrhoids seen by the gynecologist are entirely asymptomatic. The treatment of anal conditions is described.

The author's judgment as to when to operate or not in the case of fibroids of the uterus is clear cut and conservative, as is his discussion as to whether to perform total or subtotal hysterectomy for this condition. He is mainly guided by the appearance of the cervix and the absence of inflammation in this area. In 300 cervical biopsies, four early carcinomas (in situ) were found. He is not too enthusiastic about performing myomectomy, certainly much less so than either Bonney or Rubin. Operative injury to the ureters is taken up. Nonmalignant ovarian lesions and their therapy are satisfactorily described. Whether the author is too sanguine that dilatation relieves some dysmenorrheas is a matter of opinion. He performs this operation regularly under pentothal sodium anesthesia.

The important condition of carcinoma of the cervix is very thoroughly treated, and the importance of early recognition of carcinoma by means of histology is emphasized. Both Martzloff's and the strictly clinical classification of the League of Nations is discussed, as well as the analysis of operative and radium statistics. In conformity with most American authors, Te Linde treats the majority of cervical cancer by means of x-ray and radium, combined. Only in very early cases is a radical panhysterectomy without gland dissection warranted. The radiation technique is entered into in considerable detail. For corpus carcinoma, radium and abdominal hysterectomy and bilateral salpingo-oophorectomy is recommended.

Functional bleeding is treated more or less in the usual way, curettage and progesterone being the main reliances. Endometriosis is given a very detailed description, including the theory, the symptomatology, and the therapy. Operatively, much individualization is indicated. Presacral neurectomy is warranted only in patients in whom all other measures have failed. Gonorrhea and its complications are very thoroughly described, including the details of bacteriologic culture. Perhaps Te Linde might be willing to alter the statement that "those cases of gonorrhea that do not respond to sulfonamide therapy should be treated with penicillin," to first trying penicillin, since now it is so readily available. Surgical measures for residua are very detailed. I predict that this type of surgery will become rarer and rarer, as early treatment of gonorrhea will limit peritoneal infections to small numbers.

Pregnancy and its complications include the discussion of abortion in the treatment of which I am glad to see that roentgen abortion is mentioned. The operations for ectopic gestation is described in which the author mentions examination of the patient under pentothal sodium anesthesia in doubtful cases, as well as the occasional use of the peritoneoscope for both ectopic gestation and for the adequate diagnosis of small doubtful ovarian tumors, including a full description of the instruments and the techniques. For the diagnosis and treatment of sterility, insufflation of the tubes under pentothal sodium anesthesia followed immediately by dilatation and curettage does not appeal to me. There is also a very nice description of operations for implantation of tubes and ovaries as well as salpingostomy.

In describing the operation for sterilization, not only the technique, but also the laws governing the control of this operation, the psychiatric and medical indications, are very adequately dealt with. The author mentions that 26 techniques have been published. He personally prefers the Pomeroy method, but mentions a number of others including excision of the cornual tube and the Aldridge reversible operation.

A lengthy chapter is devoted to ovarian tumors and illustrated by colored plates of the gross pathology. The chapter on retroperitoneal growths is rather inadequate. A long chapter discusses the treatment of congenital absence of the vagina, with a description of several of the operative techniques. There is a satisfactory chapter on the surgical conditions of the vulva and vagina. I suggest that the author could be more radical in the treatment of kraurosis. If this were a general method, and fully adopted, it might be quite unnecessary to consider the Basset operation for removal of the inguinal glands. Among the many other conditions taken up are abdominal herniae and diastases, emergency intestinal work, use of estrogen in the menopause, for which the author prefers the introduction of pellets.

All in all, this is a very important contribution to gynecology, because it gives a very thorough, unhurried insight into the problems, a thorough discussion of the pros and cons, a very adequate and well-illustrated guide to operations. The line drawings are particularly good. I can say without reserve that not only the budding gynecologist, but the more mature specialist will read this book with pleasure and profit.

R. T. FRANK.

The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy[2] by Victor Bonney is the leisurely, very personal account of the development of myomectomy to the *nth* degree by a master technician. It is a treat to read, and contains an immense amount of information which should prove of utmost value, particularly to the budding gynecologist.

Myomectomy has always been an operation considered to involve undue risks and has usually been avoided, particularly by the occasional operator. Hemorrhage and sepsis have been the main barriers. The first distinct publication on the subject known to Bonney is that of Alexander of Liverpool, who, in 1897, published his technique, which consisted of an incision through the anterior wall through which he removed as many as twenty-five fibroids. The mortality was 9 per cent, which was as good as that of hysterectomy at that time. In the intervening years, Bonney finds that the literature, both in the United States and Britain, dealing with myomectomy, is very scant. His personal interest began in 1913. In 1923, he developed his special myomectomy clamp which stops the circulation through the uterines and the cervix. In a total of 806 myomectomies, his operative mortality has been 1.1 per cent. In 40 per cent of these patients there was a single tumor. The greatest number of tumors removed in any one patient was 225 fibroids from a uterus which had reached the size of a seven months' pregnancy. There has been a recurrence of only 2.3 per cent; not a single recurrence in patients after the thirty-fifth year. In only seven patients did the menorrhagia persist; in one requiring hysterectomy; in one, curettage. Thirty-eight per cent of those who were married and wanted to have children conceived, and in that number there was only one miscarriage. In 806 cases there was only one sarcoma, the patient dying within a few months. This is such a small percentage that I wonder whether pathologic examination of all the tumors has been routinely performed. To my knowledge, at the Mount Sinai Hospital a number of cases of sarcoma have been noted after myomectomy. In almost all of these, x-ray castration was performed, and in none did recurrence or metastases develop.

The author has also performed myomectomy in cases of adenomyoma without a single recurrence and with complete relief from excessive hemorrhage and dysmenorrhea. None of these patients conceived. In looking over his private material, Bonney finds that in the last

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[2]**The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy.** By Victor Bonney, M.S., M.D., B.Sc.Lond., F.R.C.S.Eng., Hon. F.R.A.C.S., M.R.C.P., Lond. Consulting Gynaecological and Obstetric Surgeon to the Middlesex Hospital, London; Consulting Surgeon to the Chelsea Hospital for Women; Visiting Gynaecologist to the British Postgraduate Medical School; Honorary Consultant in Obstetrics and Gynaecology to the Army, etc. First Edition. 282 pages. With 242 original drawings by the author. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York and London 1946.

twenty-five years he has performed myomectomy in 35 per cent, in the rest hysterectomy. He always considers myomectomy if the patient is under 41 years of age. He always selects it in any case where myomectomy is the lesser operation, or if the uterus might prove useful for ventrofixation in cases where colporrhaphy is indicated. (I have avoided ventrofixation since 1932 after finding that this operation is followed so frequently by ventral hernia in prolapse, and have substituted the Manchester operation instead of ventrofixation.) The author does not consider degeneration of fibroids a contraindication to myomectomy. The sole possibility of contraindication might be in the rare form of cirrsoid fibromyoma. The additional risk of myomectomy depends entirely on the local condition and the operator's experience. Decisions should also be influenced by the wishes of the patient.

The antiseptic pre-operative preparation of the skin should be extremely careful in myomectomy. "In nearly all cases of myomectomy it is advised to open the uterine cavity. . . ." He prefers a midline incision in order to have ready access to either side. In my opinion, this slight advantage is far outweighed by the increase of herniation and evisceration following midline incision. He says that it is impossible to perform myomectomy on the scale that he does without first gaining control of the arteries which supply the uterus. This was what led him to develop his special myomectomy clamp, and, in addition, to clamp temporarily the infundibulopelvic ligaments either lateral or mesial to the ovary by means of noncrushing forceps.

The remainder of the book is really a running commentary; and very simple, clear cut, and rather artistic line drawings which illustrate every step of the numerous operations performed under varying conditions of size, position, etc., of the fibroids. In all there are 220 illustrations devoted to myomectomy and adenomyomectomy, the remainder of the total 241 being used to illustrate ovarian cystectomy.

The author, whenever it is humanly possible, makes his incision in the anterior wall of the uterus after making the field bloodless by his special clamp. Fibroids, as encountered, are enucleated after the capsular layer has been found. Habitually, the uterine cavity is boldly explored for submucous fibroids or polyps, which are removed, and posterior fibroids which are found accessible are enucleated through the posterior lining of the endometrial cavity. The beds of the fibroids are closed by interrupted sutures introduced by means of the Reverdin needle.

On the other hand, if the fibroids are mainly in the posterior wall, the so-called Hood operation is utilized. This consists in a transverse incision, one-half inch behind the tubo-ovarian juncture. Through this posterior flap the fibroids are removed, the uterine cavity opened for exploration, and after myomectomy the transverse flap, which may require some thinning, is pulled over the anterior wall so that the scar is along the anterior surface of the uterus. Occasionally, when multiple small fibroids are in close juxtaposition, segments of the uterus containing these fibroids are excised (Block excision) and apparently the author does not hesitate to practically bisect the uterus down to the cervix in order to be able to remove many fibroids. The uterus is then reconstructed by comparatively few buried and deep sutures. In closing a gap in the posterior endometrium, through and through sutures, with the knots in the uterus, are used. Special attention is given to cervical fibroids which have developed alongside the vagina.

Myomectomy in pregnancy is divided into the viable and nonviable stage. In the nonviable stage the technique is like that in nonpregnancy. In the viable stage, the fetus and placenta are first delivered before application of clamps is resorted to. For adenomyomectomy the strips of affected musculature must be taken off *seriatim* until the growth has been completely excised. Here fundal excision with re-implantation of the tubes has been practiced.

The author also describes ovarian "cystectomy," which means excision of new growths from the substance of the ovary and which he considers applicable to all nonmalignant types, including dermoids, follicle cysts, chocolate cysts, multiple adenomatous cysts, and fibromas. I cannot follow his pathology as far as "multiple adenomatous cysts" are concerned. I personally have seen too many recurrences following resection performed on pseudomucinous cysts, but fully agree with him in the case of dermoids, of which I have removed as many as 10 from the two ovaries of one patient. I likewise would hesitate to resect chocolate cysts

unless they are the minute implants one sometimes encountered, as I have been obliged to reoperate too often on patients in whom this operation had been performed by others.

As far as the technique is concerned, he adds little to that I have seen commonly practiced. I must say that the suture of such a small and delicate organ as the ovary by means of a Reverdin needle seems abhorrent. For this type of reconstruction I am in the habit of using needles that the eye surgeon employs in suturing the conjunctiva.

All in all, this is a most stimulating and fascinating monograph. It shows how persistence, the experience gained on a large material, and ingenuity enable the individual surgeon to develop techniques to an undreamed-of degree of refinement and facility. However, although I pride myself on conservatism, I feel that Dr. Bonney goes somewhat too far in trying to preserve the uterus in cases of adenomyoma where, incidentally, I have run into a rare condition which I have described (intralymphatic fibromyosis) which is a slowly progressing malignancy, grossly indistinguishable from adenomyoma.

This monograph should certainly be studied by every gynecologist, and perhaps its affect on the many who, so regularly and often uncalled for, remove the uterus, may serve to reform their needless radicalism.

R. T. FRANK.

Guggisberg, editor of the **Lehrbuch der Gynäkologie**[3] has produced a 717 page volume. This textbook is Volume I of a series including Gynecology; Volume II, Obstetrics; Volume III, Obstetric Operations; brought out by a combination of the German-speaking universities of Zurich (Anderes), Bern (Guggisberg) and Basel (Koller).

In his introduction, Guggisberg mentions that the war has removed all German books on gynecology and obstetrics from the market, and therefore this combination of universities for women's clinics is getting out these textbooks to fill the gap, especially for medical students and practitioners. In this volume there are five collaborators, Guggisberg, Hintzsche, Ludwig, Müller, and Neuweiler, who take up various chapters.

The anatomy and the development are covered in rather a short sketchy chapter, illustrated by line drawings which are not fully adequate. Malformations of the uterus are well described in detail and illustrated in the usual way as well as by good hysterograms. In absence of the vagina, the modern skin graft methods and the nonoperative method for producing a vagina are not mentioned. Individual chapters on the constitution and the growth disturbances are included. The physiology, which is taken up by Guggisberg, is detailed, somewhat difficult to grasp because of lack of emphasis and over-recital of innumerable facts. This chapter is followed by one on functional disturbances which include not only those of menstruation, but also those of vaginal secretion and pain (dysmenorrhea). The methods of diagnosis are gone into in considerable detail. The apparatus for a Rubin insufflation test is the crude Sellheim syringe method with introduction of air. To my surprise, laminaria for the dilatation of the cervix are featured as a preliminary to diagnostic curettage. In hysterography, lipiodol is still recommended instead of the water soluble radio-opaque substances which are rapidly absorbed and produce no permanent peritonitic irritation. The chapter on myomas is very detailed, clear, and informative, as is the chapter on cervical carcinoma which appears to be the most striking of all. Associated tracts, intestinal and genitourinary, are given individual chapters. Not only sterility, but an excellent chapter on contraception is included. Hormone therapy, likewise physical, radiotherapy, vitamins, and hygiene of the female cover the concluding chapters. The hygiene of adolescence is well presented.

In review, I may say that every detail of gynecology and allied branches is taken up and presented for the student and practitioner. Operative therapy is merely indicated. Even if this is so, the treatment of prolapse of the uterus is very insufficient from an anatomic standpoint. On the whole, the amount of material included is huge. To me, a distinct fault is the drabness of presentation, the lack of any preference or individuality, and the complete omission of references, even by name, so that the student, when he has finished studying this book, has not the slightest idea of any historical connections or any individual preferences.

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[3]**Lehrbuch der Gynäkologie.** Bearbeitet von Prof. Dr. H. Guggisberg, Prof. Dr. E. Hintzsche, Prof. Dr. F. Ludwig, P. D., Dr. C. Müller, and Prof. Dr. W. Neuweiler. Herausgegeben von Prof. Dr. Hans Guggisberg, Direktor der Universitäts-Frauenklinik in Bern. 717 pages. Verlag Von S. Karger in Basel (Schweiz). 1946.

The book contains many marvelous macroscopic colored illustrations. These cover a large number of the commoner gynecologic conditions, certainly sufficient for any student textbook. If the rarer conditions had been illustrated by means of the same technique, the book would really pass as an atlas. On the other hand, the line drawings are distinctly crude, and the microscopic pictures are mostly unclear and appear poorly focused. Except for the colored illustrations, this book offers no advantage to the English-speaking student.

R. T. FRANK.

The second edition of Mazer and Israel's **Menstrual Disorders and Sterility**[4] appears after an interval of five years. It is designed for students and practitioners primarily, but delves far deeper into the subject than that level of presentation. The description of pituitary and ovarian function is very detailed and clear, and will prove of interest to laboratory workers as well as to practitioners.

In the chapter on dysmenorrhea, the innumerable measures published for the relief of this symptom are reviewed. Strong repeated dilatation of the cervix is recommended. Premenstrual tension, *mittleschmerz*, and amenorrhea due to pituitary disorders are described. Among other causes of amenorrhea taken up is that due to primary ovarian derangement, malfunction of the thyroid gland, adrenals, and nervous system.

Uterine bleeding is another main topic. The authors first discuss systemic causes, then local organic pelvic lesions before coming to the functional bleedings of puberty and childbearing age, as well as postmenopausal bleeding. They are to be commended for giving so thorough and detailed a description of organic pelvic lesions which may cause menorrhagia and metrorrhagia, and which must be excluded before the diagnosis of functional bleeding may be entertained.

More than 100 pages of the monograph are devoted to the subject of sterility. The influence of gross pelvic lesions, defective insemination of the cervix, and tubal factor are considered. Among the endocrine factors, amenorrhea, menometrorrhagia, anovular menstruation, even an inadequate progestin phase are discussed. In this connection I would recommend that more attention be directed to general constitutional causations, at least in evaluating the prognosis instead of focusing too narrowly upon the genital tract. Artificial insemination is discussed, including technique.

The chapters on male sterility were written by Dr. Charles W. Charny. He reports that "adequate" endocrine therapy with gonadotropins yielded good results in 10, 29, and 34 per cent of patients depending upon the nature of the semen defect. "Relative sterility" which, according to the authors, signifies "the inability to carry successfully the products of conception to term"—in my opinion is a misnomer. It is an important chapter dealing with a subject as yet not fully understood. The authors give a fair and unbiased presentation of the many facettes, conjectures, and hypotheses.

The monograph is based upon large clinical experiences, continued laboratory control, and careful study of the literature (adequate chapter bibliographies). Good judgment has been shown in not trying to subdivide and pigeon hole the many causes for symptoms into rigid classifications as so many other authors have attempted.

One might take issue with some of the therapeutic advice such as the clinical use of "water-soluble hormone of the corpus luteum," for which there is no substantiation. It might also have been well, after giving the many remedies recommended in the literature for amenorrhea, menorrhagia and metrorrhagia, dysmenorrhea, etc., to emphasize more strongly personally preferred methods which have borne the test of time. On the whole, however, this is a good book.

R. T. FRANK.

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[4]**Diagnosis and Treatment of Menstrual Disorders and Sterility.** By Charles Mazer, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to the Mount Sinai Hospital, Philadelphia, and S. Leon Israel, M.D., F.A.C.S., Instructor in Gynecology and Obstetrics, School of Medicine, University of Pennsylvania; Associate Gynecologist to the Mount Sinai Hospital, Philadelphia. Second Edition, Revised and Enlarged with 133 illustrations. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1946.

Conference on Diagnosis in Sterility,[5] edited by Earl T. Engle, is the Proceedings sponsored by the National Committee on Maternal Health for a meeting held in January, 1945. The main object of the meeting was to discuss not only the diagnosis of sterility, but also, in the main, therapy and infertility. There are twelve articles and a concluding summary of which five deal with the male and the remainder with the female.

Laboratory examinations of semen specimens by MacLeod, clinical interpretation of semen analysis by Simmons, testicular biopsy by Charny, the role of the accessory glands of fertility by Huggins, and chronic hemospermia by McDonald are included. I can agree with Rock who, in his summary, believes that the importance of biopsy can be exaggerated. The accessory glands appear to play little role in the human being.

The diagnosing of endometrial biopsy by Hertig is a very well illustrated and conservative contribution. Interpretation of basal body temperature curves by Tompkins is of interest. The interpretation and evaluation of tubal patency tests by Normal Miller are of interest, as is the so-called "pelvic congestion" in relation to sterility by H. C. Taylor, Jr. Rock's summary, although at times flippant, is an excellent critique.

R. T. FRANK.

Obstetrics

Haultain and Kennedy have done an excellent job in the revision of their **Practical Handbook of Midwifery and Gynaecology.**[6] The text is direct and concise, and the material is quite up to date with the noteworthy omission of penicillin as a therapeutic agent in puerperal and gynecologic infections. The operations to deliver are described fully; gynecologic surgery is limited, however, to a very brief presentation. The manual should be of much assistance to the returning soldier physician who wishes for a quick review of these two subjects.

PHILIP F. WILLIAMS.

The Transactions of the Pacific Coast Society of Obstetrics and Gynecology[7] has just appeared. There were no meetings or transactions in 1944 or 1945. In addition to a number of purely casuistic clinical articles, there is an interesting description of the recovery of primate eggs and embryos by Carl Hartman.

R. T. FRANK.

Leon's **Obstetric Symptomatology**[8] is an 800 page textbook dealing with the symptoms and differential diagnosis in obstetrics. It is meant strictly for clinical practice. The subject matter, in a very detailed and copiously illustrated fashion, describes the changes occurring in pregnancy, taking up the individual, the body fluids, hormonal changes, and then individual organ systems. It covers the fetus at term, the maternal pelvis, both normal and deformed, fetal positions, ten original cross sections of uteri at term, external and internal palpation, and x-ray of the fetus. The usual clinical examinations and pelvimetry, both external and internal, are described in a most detailed fashion. Radiopelvimetry, both har-

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[5] **Conference on Diagnosis in Sterility.** Sponsored by the National Committee on Maternal Health, January 26 to 27, New York City. Edited by Earl T. Engle. 237 pages. Charles C Thomas, Springfield, Illinois. 1946.

[6] **A Practical Handbook of Midwifery and Gynaecology for Students and Practitioners,** by W. F. T. Haultain, O.B.E., M.C., B.A., M.B., B.Ch., Obstetrician and Gynaecologist, Royal Infirmary, Edinburgh; Consulting Gynaecologist, Leith Hospital; Lecturer in Clinical Midwifery and Gynaecology, University, Edinburgh; and Clifford Kennedy, M.B., Ch.B., Assistant Obstetrician and Gynaecologist, Royal Infirmary, Edinburgh; Lecturer in Midwifery and Gynaecology, School of Medicine of Royal Colleges, Edinburgh. Third Edition, 380 pages. 47 illustrations. The Williams and Wilkins Company, Baltimore. 1946.

[7] **Transactions of the Pacific Coast Society of Obstetrics and Gynecology.** Volume XIII, Year 1943. 159 pages. Western Journal of Surgery Publishing Co. 1946.

[8] **Semiologia Obstetrica.** Treinta Y Seis Clases Practicas. Diagnosticos Y Diagnosticos Diferenciales. By Juan Leon, Profesor adjunto de Clinica Obstétrica de la Facultad de Ciencias Médicas de Buenos Aires; Docente libre de Clinica Ginecológica; Jefe de Clinica de la Clinica Obstétrica y Ginecológica "Eliseo Cantón"; Médico de los Hospitales; Jefe de la Guardia Obstétrica. 797 pages. Con 501 Ilustraciones (45 en colores, de las cuales 7 láminas en citocromía) "El Ateneo," Buenos Aires. 1946.

mony and disproportion between fetus and mother, is discussed. The early clinical diagnosis of pregnancy is gone into, and also the fact that x-ray diagnosis is impossible until the fourth or fifth month. He then takes up biologic diagnosis, and goes into very many tests including the Frank-Berman test which he concludes is not sufficiently characteristic and clear cut, based on the investigation of one of his pupils who apparently focused more attention on the microscopic histology than upon the gross appearance of the ovaries. In turn, the various complications encountered in pregnancy, particularly fibroids and ovarian tumors, are described. The recognition of fetal death is discussed without mention of our blood test which, after the fourth month, discloses fetal death within twenty-four hours. The first portion of the large volume is concluded with presentation of prenatal care.

In part two, which is devoted to differential diagnosis, a very extended presentation of pelvic difficulties is given, including both anatomic and clinical evidence. Finally, pregnancy toxemias are discussed.

It is rather amazing that in a book which covers such a large amount of ground with so much detail, and takes cognizance of the immense amount of literature which has accumulated, no references whatever are given. The material is well digested and clarified. A large personal clinical material is included. The book is almost encyclopedic in scope, and therefore the lack of references to the literature is to be deplored.

R. T. FRANK.

Miscellaneous

Early Ambulation and Related Procedures in Surgical Management[9] by Leithauser is a forthright and interesting monograph which places the procedure, which is gaining more and more adherence, upon a sound physiologic and well-planned basis. This by no means implies that I agree fully with the enthusiasm of the author because, to me, who heard Emil Ries and Herman Boldt in 1899 and 1907, respectively, advocating early rising, it was a personal experience connected with the beginning of my surgical career. Boldt, in 1907, would report these cases at the New York Obstetrical Society meeting where he usually aroused marked opposition.

The monograph is based on 2,047 cases, of which 1,840 were laparotomies and of which 840 patients were out of bed within three to four hours after operation. The total death rate was 14, amounting to 0.68 per cent. The object of this procedure is to control and prevent respiratory, circulatory, gastrointestinal, and wound complications, and simultaneously to stimulate rapid recovery. The patients are taken out of bed as early as two or three hours postoperatively. They go to the toilet on the second or third time they are out of bed. They are given soft diet within twenty-four to thirty-six hours if they so desire, and the ordinary appendices cases return to their homes on the second day. A drained cholecystectomy usually returns home within the week. What would be of real interest and importance would be to obtain statistics as to how soon these early rising patients return to their regular occupation. (I wonder whether the enthusiastic author takes into account that at the present and under present conditions, help and supervision at home may be entirely lacking. I repeatedly encounter patients today who beg to be kept in the hospital for a few additional days because they can get no assistance whatever at home.)

In discussing the physiology, the author mentions the report by Baker, et al., from the Mayo Clinic, published in 1940 and based on 172,888 surgical cases with 1 per cent thrombophlebitis and one fatality from this cause in 500 cases, which led these authors to the use of heparin and dicoumarol. Leithauser's chapters on the physiology of pulmonary, circulatory, gastrointestinal symptoms postoperatively, and the effect of early rising upon them, are excellent. The author emphasizes the importance of preventing dehydration. Preoperatively, a small nasal syphon suction apparatus is introduced and retained for twenty-four hours. A liter of water with 5 per cent glucose is given preoperatively; in the first twenty-four hours

[9] **Early Ambulation and Related Procedures in Surgical Management.** By Daniel J. Leithauser, M.D., F.A.C.S., Chief of Surgery, St. Joseph Mercy Hospital, Detroit, Michigan. 232 Pages. Charles C Thomas, Springfield, Illinois. 1946.

postoperatively, 4 liters of water is given with 9 Gm. of sodium chloride, partly by subcutaneous route. No enema or cathartics are given on the day of operation. As contraindication to early rising, only profound shock, hopeless conditions as carcinoma, midline rectus incision, or an insecure suture technique would be considered. No morphine is given after the first twenty-four hours. The first bowel evacuation can wait for several days or up to a week after operation. Catheterization is rarely necessary in patients who get up early. In cystocele operation, a retention catheter is kept in situ for twenty-four hours, and yet these patients are treated as early ambulants.

Several interesting chapters deal with the operative techniques of the author, particularly the placing of his incisions. Transverse or gridiron incisions are advocated. The peritoneum and transversalis is sutured with 000 chromic catgut and for fascia, 32 alloy steel is used. A subcuticular metal suture is used for the skin. Drainage of either appendix, gall bladder, or any other intra-abdominal incision, if indicated, does not prevent early rising. An analysis of the operations performed and a detailed analysis of all of the fatal cases are given.

Thorough study of this monograph by all surgeons who are not yet converted to early ambulation is suggested.

R. T. FRANK.

Penicillin, Its Practical Application,[10] which appeared under the general editorship of Professor Alexander Fleming, is really a *must* for anyone who intends to produce, market, or use penicillin widely. It is an all-British product, having twenty-eight contributors whose independent views do not show too much conflict. The book is intended for the practitioner, and shows him how to use penicillin to the best advantage. It likewise includes two chapters on dental and veterinary practice.

The senior author, Fleming, writes an introduction and a chapter on "Bacteriological Control of Penicillin Therapy." Few will agree with his remark, "My own contribution to this book is small. . . ." He recommends that it is "better to give more than enough than too little" because to all intents and purposes penicillin is a nontoxic substance. He describes how he discovered it in 1928 as a contaminant in a culture plate of staphylococci; how the flora grows in chains; how penicillin was concentrated 1,000 times in 1940; how the International Unit which equals 0.0006 mg. of pure crystalline sodium salt of penicillin II (United States, penicillin G) was evolved. This corresponds to 5,000 units, equalling 3 milligrams in weight.

It is quite impossible to discuss the really enormous amount of facts contained in this text and source book in the form of a review. A few chapters will be mentioned. Chemistry (Bacharach and Hems) shows that the substance, if the β-lactam formula is accepted, is a monocarboxylic acid, to be used as a sodium or calcium salt. The production and manufacture have now become a huge industry. Surface growth has been abandoned in favor of deep growth in 2,000 to 10,000 gallon tanks. The main steps are aeration, agitations, and asepsis. The production h.. been greatly accelerated by the use of "corn steep liquor."

Under pharmacy (Berry), the lack of toxicity, the sterility, the use of either calcium or sodium salt, the storing at less than 50 degrees Centigrade, the drying and freezing at pH 6.5, the incompatabilities (mainly aqueous sulfonamide solutions strong alcohols), and the various preparations such as aqueous, oily, cream, unguents, and troches are described.

The pharmacology by Garrod is important. Among other things, it shows that 60 per cent of penicillin is excreted in the urine; that unless the blood level is raised and unduly high, no entrance into the cerebrospinal fluid is observed, and that oral dosages must be about five times that of parenteral.

The chapter on bacteriological control of penicillin therapy by Fleming shows the rapid method of assay which is now essential during the course of mass production; also the estimation in body fluids, urine, etc.

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[10]**Penicillin. Its Practical Application.** Under the General Editorship of Professor Sir Alexander Fleming, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S., Professor of Bacteriology in the University of London, St. Mary's Hospital, London. 380 pages. The Blakiston Company, Philadelphia. 1946.

Hughes takes up methods of administration, which are now generalized and well known, the continuous intravenous drip method, parenteral and local, either in cavities or on surfaces.

The clinical application of penicillin begins with the prophylactic use by Parritt and Mitchell; application in generalized infections (Hudson); bacterial endocarditis (Christie). It then takes up the individual uses in surgery and medicine—chest surgery, wounds, and gas gangrene, burns and plastic surgery, orthopedic surgery and fractures, osteomyelitis, hand infections, abdominal infections, sepsis of the newborn, brain and meningeal infections, venereal diseases, ophthalmology, otorhinolaryngology, dental and oral infections, penicillin in animal diseases, and a final chapter on penicillin and the general practitioner.

I have left for the last, and out of order, the chapter on Obstetrics and Gynecology by Leslie Williams, as this, after all, is of most interest to readers of this JOURNAL.

In obsterics, prenatally it probably does not bring on premature labor or the menses, as has been frequently suspected. It naturally is used in gonorrhea of the pregnant women, the custom being to give 100,000 units in beeswax oil at night and 50,000 units in the morning so as not to obscure a developing syphilis. In syphilis of the pregnant woman, 500,000 units should be given daily in beeswax oil for seven days; also 10 injections of neoarsphenamine, at four-day intervals, and 10 injections of a bismuth salt. In 14 syphilitic women so treated, no stillbirth occurred. There is a definite indication, both prophylactically and postoperatively, in risky cesareans, keeping it up for seven days; in obstetric cases complicated by general illnesses and hemorrhages or suspected infection; also in postpartum infections, indication for it is clear. To prevent ophthalmia neonatorum 2,500 units per c.c. of solution are a safe prophylactic; for cracked nipples, 200 units per gram of vehicle.

In gynecologic conditions, it is indicated for abdominal wall suppuration, postoperatively if blood stream infection develops, in pelvic cellulitis, in adnexal inflammations and gonorrhea generally; in pyogenic infections of the vulva as a salve. The author also indicates that it might be useful as a bougie in the cervical or vaginal canal.

There is no question that the introduction of penicillin and other antibiotics have completely changed the treatment of many infections. In none of these is it more striking than in gonorrhea where it has completely superseded the abhorrent and dangerous cervical treatment formerly needed.

This book can be most highly recommended, even though, because of the newness of penicillin as a therapeutic agent, many and rapid changes may be anticipated in every branch of the subject.

R. T. FRANK.

Benda has written an authoritative monograph on **Mongolism and Cretinism**[11] which is based on a study of the clinical manifestations and the pathology of pituitary and thyroid deficiency, and mainly on 46 autopsies. According to the author, there are 60,000 living mongoloids in this country. He finds one mongoloid in 285 dispensary children. It was recognized as early as 1907, as a growth deficiency by Arthur Schüller, who called it "congenital acromicria," the opposite of acromegaly. The mongoloid pituitary is damaged during fetal life. The characteristics which make all mongoloid children appear as if they were brothers and sisters are due mainly to skull deficiency, among the other growth changes that occur. The pituitary gland of a mongoloid is small, in contradistinction to that of a cretin, whose pituitary is large. Examination of 46 mongoloid pituitaries showed only three normal. Fifty-four per cent showed castration cells. If the thyroid is found to be colloid, there is a predominance of eosinophiles in the pituitary.

The various endocrine glands are discussed in detail, both for mongoloid and the cretin. The author believes that to avoid mongolism, the pregnant mother should be treated. Direct

[11] **Mongolism and Cretinism.** A Study of the Clinical Manifestations and the General Pathology of Pituitary and Thyroid Deficiency. By Clemens E. Benda, M.D., Director, Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham, Mass., Instructor in Neuropathology, Harvard Medical School, Assistant in Psychiatry, Massachusetts General Hospital, Lecturer, Postgraduate Seminar, Massachusetts Department of Mental Health. 310 pages. 101 illustrations. Grune & Stratton, New York. 1946.

treatment of mongolism is impossible until we obtain an active pituitary gland substance which as yet has not been possible. He believed that if the pituitary of immature animals could be obtained, such an extract might perhaps be developed.

R. T. FRANK.

The author of this book, **Sex, Marriage and Family,**[12] has been vitally interested in the problems of the marriage relationship, and is thoroughly qualified to discuss these topics. Dr. Rice has gathered together in one volume the essence of his many contributions to benefit the lay public on these questions. Such phases of marriage as birth control, reproduction, and the necessary adjustments in marriage for incompatibility, frigidity, impotence, and sterility are discussed. The changes in relationships as married life proceeds, the raising of a family, changes in economic situations, the menopause, and infidelity are dealt with fully and clearly. An outstanding section of the book is the consideration of the choice of a mate, while the problems of sex and marriage in relation to the war are fully discussed.

The book has been written in such a spirit of dignity and frankness as to make it an outstanding volume on the subject. It can be highly recommended for the instruction for those of the lay public who may have marriage problems to face.

PHILIP F. WILLIAMS.

This small volume, **Sex Problems of the Returned Veteran,**[13] by Dr. Kitching, deals frankly and wisely with the problems created for many married people by the recent war. It may be read with profit by the husband and wife, their parents, advisers, and medical counselors, for it explains clearly the effect of the artificial and unnatural separation by war upon both partners. Dr. Kitching discusses separation anxiety and its physical, emotional, and spiritual results. The wife's problems are no less sympathetically reviewed than those of the soldier who has served on foreign soil. The psychological impact of the reunion anxiety are analyzed and the problems of remarriage and readjustment and their solutions are skillfully handled.

Such an informative book should be of inestimable value to those in the profession to whom the returned soldier and his wife may turn for help on their sex problems.

PHILIP F. WILLIAMS.

This detailed compendium on **Regional Anesthesia**[14] presents the work of Dr. Pitkin, with contributions by present-day workers on all types of regional, refrigeration, spinal, and epidural anesthesia. The editors and contributors are well qualified in their respective lines, and have clearly, completely, and concisely covered the field from the standpoint of anatomy, rationale, and technique. The description of the text has been enriched by the great number of illustrations. The modern concept of, and necessity for, regional blocks in surgery and therapy are convincingly handled. The index is complete and well organized. Of particular interest to obstetricians and gynecologists is the section on continuous caudal block, its indications, contraindications, and accomplishments. While the text appears to be primarily of value to the specialist in anesthesia, it is an excellent reference work for the general or specialist surgeon.

PHILIP F. WILLIAMS.

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[12]**Sex, Marriage and Family,** by Thurman B. Rice, A.M., M.D., Professor of Bacteriology and Public Health, Indiana University School of Medicine; Author of "Sex Education Series," American Medical Association; Chairman of Joint Committee on Health Education of National Educational Association and the American Medical Association, J. B. Lippincott Company, Philadelphia and New York. 1946.

[13]**Sex Problems of the Returned Veteran,** Howard Kitching, M.D., Foreword by Ernest R. Groves, Professor of Sociology, University of North Carolina, 124 pages, Emerson Books, Inc., New York. 1946.

[14]**Conduction Anesthesia, Clinical Studies** of George P. Pitkin, M.D., F.A.C.S., F.I.C.A., edited by James L. Southworth, M.D., and Robert A. Hingson, M.D., with chapters prepared by the following collaborators: Winifred Pitkin, M.D., M.R.C.S.; A. R. McIntyre, M.D., Ph.D.; Frederick M. Allen, M.D., F.A.C.P.; Waldo B. Edwards, M.D.; Louis A. Palmer, M.D., F.A.C.S.; William T. Lemmon, M.D., F.A.C.S.; Lyman W. Crossman, M.D., F.A.C.S.; Henry G. Hager, Jr., M.D. 930 pages, with 606 illustrations. J. B. Lippincott Company, Philadelphia, London, Montreal. 1946.

The present fourth edition of Meredith's **Hygiene**[15] has been rewritten to incorporate the public health advances of the war period. The book is intended for the college student, but it is equally appropriate to the interested general public at large, since emphasis is made on the fact that individual health means good community health.

The material is logically arranged, and after taking up the general health problems of the human body and the body politic, the author discusses infections, the degenerative diseases, some surgical situations, accidents, with an excellent presentation of habit-forming drugs.

The seventh part of the book details the aspects of everyday personal hygiene, in which the important part of nutrition is stressed. The gynecologist will approve of the considerable space and scientific exposition of the reproductive processes, as well as the section on cancer.

Such a book merits a place in the family library, as well as in the college curriculum.

PHILIP F. WILLIAMS.

[15]**Hygiene**, a textbook for college students on physical and mental health from personal and public aspects, by Florence L. Meredith, B.Sc., M.D., Professor of Hygiene and Public Health, Tufts College. Fourth Edition. 805 pages, 155 illustrations. The Blakiston Company, Philadelphia and Toronto. 1946.

Department of Reviews and Abstracts

Selected Abstracts

Pregnancy, Physiology

Baird, Dugald: The Influence of Social and Economic Factors on Stillbirths and Neonatal Deaths, J. Obst. & Gynaec. Brit. Emp. **52**: 359, 1945.

In a previous paper prematurity was shown to be an important cause of stillbirth and neonatal mortality in Social Classes III, IV, and V of the community. In Scotland the incidence of prematurity is greater than in England, and the excess of neonatal mortality in Scotland is due largely to prematurity. Prematurity has an incidence almost twice as high in Social Classes III, IV, and V as in Classes I and II. In the former classes 50 per cent of the prematurity is "unexplained" in relation to any definite obstetric condition; the most common obstetric condition associated with prematurity is eclamptic toxemia and this is twice as common among the poor as among the well-to-do. Further studies have shown that the incidents of stillbirths has fallen steadily in Scotland, as well as in England and Wales since 1939. The fall has been greatest in those cases of unknown cause and those due to trauma and toxemia. The neonatal deaths in the first three days of life (which are due chiefly to the same factors as stillbirths) have also shown a lower incidence since 1939, while the incidence of infant deaths at 4 to 28 days of age, due chiefly to infection, has shown comparatively slight reduction. Since the incidence of prematurity cause unknown, toxemia and congenital debility of the newborn has been much higher in Social Classes III, IV, and V than in Classes I to II, the evidence indicates that the reduction in stillbirths and neonatal mortality is due to the improvement of the social condition of the poorer classes, and especially to improved nutrition, better employment, higher wages, and better distribution of milk and other essential foods under wartime regulations. This wartime experience suggests that with further improvement in nutrition and in obstetric care, a further decrease in stillbirth and neonatal mortality rates will occur. How far the high stillbirth and neonatal mortality rates in the poorer classes have been due to faulty diet during pregnancy and how far to undernourishment in youth with resulting poor physique, it is difficult to determine. In the former case, the condition can be corrected quickly, in the latter only by a long-term policy.

HARVEY B. MATTHEWS.

Hudson, Gwen S., and Rucker, M. Pierce: Spontaneous Abortion, J. A. M. A. **129**: 542, 1945.

The authors report on their statistics in 1,000 consecutive pregnancies. Ninety-four spontaneous and 68 threatened abortions occurred in this group. Treatment with bed rest and progesterone was followed by recovery in 43 per cent of the cases. Three of the patients that were treated successfully had deformed babies. Falls and intercurrent infections were of no etiologic consequence in this series. Pelvic inflammatory disease was encountered three times, but two of these patients aborted. Overweight patients, those with low basal metabolic rates, and those who have a history of sterility were prone to abort; 44.1 per cent of the patients who aborted had retrodisplacement of the uterus on postpartum examination, as compared with 26.9 per cent of those who had full-term deliveries.

WILLIAM BERMAN.

Abortion

Stefancsik, S.: Etiology of Abortions, Monatschr. F. Geburtsh. u. Gynäk. **119**: 23-33, 1945.

The author maintains that when abortion occurs in the presence of genital hypoplasia, the cause is imperfect development of the cervix. That the cervix is an important cause of abortions may be seen from the cases of abortion which follow amputation of the cervix, injuries and tumors of the cervix, and from comparative obstetrics in animals. As a prophylactic measure, in cases of defective development of the cervix, the author recommends treatment before pregnancy by means of hormones as well as vitamins, regulation of the mode of living, etc.

J. P. GREENHILL.

Anesthesia, Analgesia

Onofre de Araujo, J., and Nobrega, M.: Present Status of Obstetric Anesthesia, An. brasil. de ginec. **19**: 345, 1945.

The advantages of close collaboration between obstetricians and anesthetists in the choice of anesthetic are stressed. Obstetric anesthesia differs considerably from surgical anesthesia because, besides suppressing pain, the presence of the fetus in intimate connection with the maternal system and the special conditions of the muscular birth canal, which must be preserved during labor and after delivery, requires special consideration. After a review of different methods of analgesia, of their advantages and disadvantages, the authors recommend the use of antispasmodic drugs during the first stage followed by cyclopropane-oxygen administration during the expulsion period on account of its high percentage of oxygen. For operative deliveries, the authors favor general anesthesia only for operations of short duration, such as version and extraction. For cesarean section spinal anesthesia is considered by the authors to be the method of choice when used by skilled anesthetists. Peridural anesthesia is not advocated by the authors.

The advantages of local anesthesia for normal labors, and particularly for forceps deliveries, are stressed. According to Brazilian bibliography fewer accidents of the lower birth canal are liable to occur with this type of anesthesia than any other, due to greater perineal distensibility permitted by local anesthesia.

J. P. GREENHILL.

Editorial—Anesthesia for the Pain of Uncomplicated Childbirth, Anesthesiology **6**: 410, 1945.

The medical profession and their allies are still striving for the "perfect" analgesia and anesthesia for the relief of the travail of childbirth. This effort was begun some ninety-eight years ago and bids fair to continue for another ninety-eight years before a completely satisfactory solution of the problem shall have been accomplished. During all these years every new anesthesia or technique introduced into the practice of surgery or used for the relief of pain has been tried in obstetrics, beginning with chloroform in 1847 and culminating with continuous caudal in 1945. Varying degrees of success has crowned these efforts. Despite the overflowing enthusiasm of certain obstetricians and the tumultuous acclaim of the lay press, the perfect obstetric analgesia and anesthesia has not been discovered. In fact, such enthusiasm plus the "half-baked" journalistic propaganda on painless childbirth has created a problem within its own sphere. In retrospect, we might divide the sum total of all efforts into "eras" and call them the "chloroform era"; the "twilight sleep era"; the "barbiturate amnesia era"; and finally the "caudal anesthesia era." Spinal anesthesia has been "sandwiched in" in practically all of these eras but, due to the hazards involved, it has never become a universal method. The advantages and disadvantages of continuous caudal anesthesia are still being debated by the conservatives.

That the method has distinct advantages cannot be doubted; that its disadvantages are many and often extremely hazardous to the mother cannot be denied. Furthermore, the technique of its administration is exacting and special attention is required by the patient. All of these obstacles add up to a problem that cannot be satisfactorily solved under present-day conditions in our hospitals. The lay press further complicates the picture by claiming "heavenly oblivion to the travail of parturition," thus encouraging the patient to demand something that she cannot get. Result—disillusionment and anguish on the part of the patient; disgust and vexation for the doctor. In conclusion, the author states: "From the standpoint of ideal conditions, the medical profession and its pain-controlling specialists, the anesthetists, cannot be highly satisfied or pleased with a review of their achievements in controlling the pangs of parturition, and eagerly welcome any suggestion of a satisfactory approach to the perpetual problems of painless childbirth."

HARVEY B. MATTHEWS.

Rabago, José: Anesthesia in Cesarean Section, Gac. méd. de México 74: 591-600, 1944.

According to the author, spinal anesthesia given according to the described technique and respecting strictly its contraindications, is the anesthesia of choice.

The contraindications are cardiac insufficiency, even if it is slight, maximal arterial pressure below 105 mm. due to any cause whatever, and hemorrhage during pregnancy or labor.

The following details of technique must be observed. (1) Lowest possible puncture, i.e., between the fourth and fifth or between the third and fourth lumbar vertebrae. (2) Puncture and injection with the patient sitting up and then changed to dorsal decubitus until frank signs of anesthesia appear in the lower extremities. (3) Injection of 12 to 15 centigrams (depending on the weight of the patient) of novocain, scurocain, or procain dissolved in 2 c.c. of cerebrospinal fluid. (4) Avoidance of escape of cerebrospinal fluid during preparation of the solution. (5) Subcutaneous injection of an ampule of cardiazol-ephedrine immediately after injection of the solution. (6) Trendelenburg position until the moment of opening the peritoneum. (7) Constant observation of pulse and arterial pressure to administer in time the necessary cardiac stimulants during the operation.

The author has had only one death that could be charged to spinal anesthesia: the injection of cardiazol-ephedrine was overlooked and death occurred twenty minutes after the anesthetic was given.

Inhalation anesthesia should be used in cases in which spinal anesthesia is contraindicated and the general condition of the patient allows it. Intravenous anesthesia with barbiturates endangers the life of the fetus. Epidural anesthesia is now being studied, but is not devoid of risks. Local anesthesia is innocuous and must be used in cases of grave visceral insufficiency, intense anemia, hypotension, etc. Its generalized use is desirable.

J. P. GREENHILL.

Cancer, Malignancies

Graffagnino, Peter, and McFetridge, Elizabeth: Carcinoma of the Cervix. An Attempted Follow-up Study of 500 Cases, New Orleans M. & S. J. 98: 307, 1946.

A follow-up study on 500 women with carcinoma of the cervix covering a period of five and one-half years is reported. Of this group 183 were white; 317 Negro. Known to have died during the five and one-half year period are 358 patients from the total number, and 39 are known to be alive for periods varying from seven to twelve years after treatment. Of 29 patients with carcinoma of the cervical stump there are four survivors.

The histologic types were as follows: epidermoid, 4 per cent; adenocarcinoma, 7 per cent; squamous, 23 per cent; transiditional, 34 per cent; and carcinoma (type not specified), 31 per cent. The entire group studied from the standpoint of "Grade" according to the League of Nations' classification was as follows: Grade One, 7 per cent; Grade Two,

31 per cent; Grade Three, 50 per cent; Grade Four, 12 per cent. The difficulty of accurately grading these patients is emphasized. As to the correct classification of grading, one will more often be correct if he classifies the patient as the more advanced type.

The treatment plan for carcinoma of the cervix at the Charity Hospital utilizes the technique of several investigators. X-ray therapy is an essential part of the radiation treatment and is not an auxiliary measure.

This report is based on 716 unselected cases of cervical carcinoma. The absolute three-year survival rate for the group is 37 per cent and the five-year survival period is 28 per cent. The authors are convinced that the highest salvage in all "Grades" of carcinoma is obtained from radiation therapy, no surgery being indicated in the majority of cases.

WILLIAM BICKERS.

Glatthaar, E.: Leucoplakia and Squamous Epithelial Carcinoma of the Portio, Monatschr. f. Geburtsch. u. Gynäk. **120:** 33-45, 1945.

The author emphasizes that the clinical picture of leucoplakia may be produced by a number of different histologic changes. He differentiates between benign and malignant leucoplakias. The latter is a superficial type of carcinoma. Heretofore, no one has succeeded in proving a malignant transformation of a cervical leucoplakia by histologic study. Such a change was demonstrated by the author in a 37-year-old woman both by colposcopic and histologic examinations performed at frequent intervals during a period of eighteen months. This case is important in presenting data on the development of squamous-cell carcinoma of the cervix and so-called atypical benign epithelium of the cervix. The author maintains that colposcopic and histologic studies must be made in cases where changes appear in the cervix.

J. P. GREENHILL.

Donaldson, Malcolm: Some New Facts Concerning the Prognosis and Treatment of Carcinoma of Cervix by Radiation, Proc. Roy. Soc. Med. **39:** 10, 1945.

The author divides his tumors into two types: the differentiated which he calls anaplastic squamous, in which the cells when young resemble normal basal cells, but when growing old they either undergo normal keratinization giving rise to typical cell nests or they undergo abnormal keratinization giving rise to an aggregation of basal cells round a necrotic core. In undifferentiated tumors called anaplastic parakeratotic, the cells when young are capable of active mitosis but degenerate as they get older by a process of cytoplasmic condensation or by nuclear disintegration. The differentiated tumors predominate in the early stages and the undifferentiated tumors in the late stages.

The author has attempted to work out the prognostic index of certain tumors by a quantitative study of postradiation sections for comparison with the pre-radiation section. Counts are made of resting cells, mitotic cells, differentiating cells, and degenerating cells. All counts are plotted on a graph. Biopsies are then taken on at least two occasions after the treatment has begun. The histologic evaluation is made within three weeks of beginning of treatment. A chart is given showing the number of agreements and disagreements between the clinical and histologic evaluation of treatment.

WILLIAM BERMAN.

Cesarean Section

Ricci, James V., and Marr, James P.: The Physick-Sellheim Principle of Extraperitoneal Cesarean Section, Am. J. Surg. **71:** 3, 1946.

The authors present a series of 175 cases of extraperitoneal cesarean sections with a brief analysis of the mortality, morbidity and complications encountered. A technique is described which divides the extraperitoneal operation into two major steps—(a) the liber-

ation of the anterior peritoneal fold from the upper bladder surface and dome; (b) the liberation of the posterior peritoneal fold from the posterior surface of the bladder and lower uterine segment. The steps are shown by 19 well-illustrated drawings.

JAMES P. MARR.

Sala, S. L.: Prophylactic Intraperitoneal Sulfonamide Therapy in Cesarean Section, Semana méd. **1**: 354-358, 1945.

The author presents 21 cases with ovular infection operated upon by cesarean section followed by intraperitoneal instillation of sulfonamides, without mortality. He has collected from the literature 185 contaminated cases treated with the sulfonamides with a 0.5 per cent mortality due to peritonitis; this figure is evidently lower and minimal when compared with the same kind of cases treated by other procedures. If this success continues, greater optimism for late cesarean section will lead more frequently to a test of labor and thus to more vaginal deliveries. To confirm definitely the optimistic figures offered by the method, he requests other authors to publish their clinical cases.

J. P. GREENHILL.

Infante, Thomas R.: Hemostatic Cesarean Section in a Case of Severe Placenta Previa, Rev. médica cubana **56**: 179-183, 1945.

The author reports that the patient under consideration who was in shock was given 500 c.c. of gum acacia serum, and then a blood transfusion. A vaginal examination was made just before the operation. The author emphasizes that it is imperative to have another transfusion ready if such an examination is to be made. The low cervical cesarean section is strongly recommended by the author because Greenhill and Bloom pointed out that the resulting scar following cervical cesarean section is sufficiently strong to withstand the strain of subsequent labors. This type of cesarean section requires rapid, expert action by the surgeon. The use of the sulfanilamides is suggested for preventing infection.

J. P. GREENHILL.

Endocrinology

Held, E.: The Follicle Stimulating Action of the Urine of Puerperal Women Is Due to a Hypophyseal Substance, Monatschr. f. Geburtsch. u. Gynäk. **119**: 214, 1945.

The author investigated the fundamental difference which exists between the follicle-stimulating action of castrate urine and that of urine from pregnant women. Injections of the former into guinea pigs lead to the growth of many follicles while injections of urine from pregnant women resulted in the development of only a few follicles. Earlier research had revealed that the action of the pregnant cervix is due to a substance from the anencephalus-pituitary system, generally designated as pituitary. Based on this evidence the urine of puerperal women was studied for its gonad-stimulating effect. It was found that the follicle-stimulating of this urine is the same as that of the urine of pregnant women. Hence, we are dealing with a gonadotrophic hormone of chorionic origin and not one from the pituitary.

J. P. GREENHILL.

Thermogenic Effect of Progesterone, Lancet **2**: 663, 1945.

Variations in waking temperature are so closely linked with the phases of the ovarian cycle that they probably depend upon ovarian secretion. The administration of extracts of whole ovary and of follicular fluid to a series of oophorectomized animals and menopausal women resulted in no effect on the waking temperature. Similarly, there was no effect upon the waking temperature upon the administration of natural estrogens.

On the other hand, it was possible to raise the temperature by an administration of progesterone. These observations suggest that the effect of progesterone extends beyond the endometrium to the thermal regulatory mechanism.

J. P. GREENHILL.

Endometriosis

Medina, J.: Internal Endometriosis. Its Relationship With Carcinoma of the Body of the Uterus, An. brasil de ginec. **10:** 189-197, 1945.

Carcinoma in the presence of internal endometriosis is rare. The author reports three cases which proved the transition from endometriosis to corporeal carcinoma. He accepts Robert Meyer's criterion that "the glands showing carcinomatous changes should be surrounded by cytogenous tissue." Seven illustrations prove the author's contentions.

J. P. GREENHILL.

Arenas, N., and Blanchard, O.: Perforating Endometriosis of the Posterior Fornix, An. brasil de ginec. **10:** 129-135, 1945.

The author reports a case of perforation of endometriosis of the posterior fornix with involvement of the rectovaginal septum and inflammatory lesions of the adnexa. An operation was performed during which both tubes and ovaries were removed.

J. P. GREENHILL.

Balfour, D. C., Jr.: Endometrioma of the Urinary Bladder. Report of Five Cases, Proc. Staff Meet. Mayo Clin. **20:** 129, 1945.

The author reports five cases of endometrioma of the bladder treated at the Mayo Clinic. All patients had urinary symptoms. All five patients had undergone previous pelvic operations. The author warns against substitutional hormonal therapy after artificial menopause for relief of this condition.

WM. BERMAN.

Gynecology

Kovacs, F.: The Significance, Diagnosis, and Treatment of Female Genital Tuberculosis (Experience in 191 Personal Cases), Monatschr. f. Geburtsch. u. Gynäk. **116:** 24, 183, 1943.

A personal series of 191 private cases of genital tuberculosis in women proves that this disease occurs more frequently than is generally supposed. Curettement and histologic examination of the curetted material are the most important methods of making a diagnosis. Since sterility is the rule in cases of genital tuberculosis, the endometrium should be studied in all cases of sterility and menstrual disturbances. There is no danger of spreading the tuberculosis if the curettement is properly performed.

Conservative therapy is ineffective in the treatment of genital tuberculosis. The proper therapy is surgical removal of the uterus and tubes. Since the patients are sterile anyway, no harm is done. The ovaries may be retained. The presence of tuberculosis elsewhere in the body, such as in the lungs, is no contraindication to operation, provided the operation will not seem to be too difficult.

J. P. GREENHILL.

Gynecologic Operations

Guenin, R.: The Madlener Technic of Sterilization, Monatschr. f. Geburtsch. u. Gynäk. **116:** 172-173, 1943.

At the Geneva Woman's Clinic, 135 Madlener sterilizations were performed, with the Walthard modification. The indications were as follows: eugenic and social indications, 24.8 per cent; obstetric and gynecologic, 25.2 per cent; and strict medical reasons, 50 per cent.

The only complication in this series was a case of ileus observed ten months after the operation. The patient died from peritonitis. No other disturbances were observed following the operations.

J. P. GREENHILL.

Bertrand, I., Mazars, G., and Godet-Guitlain, J.: Electro-Encephalographic Changes Associated With Uterine Curettage, Presse méd. **53**: 352, 1945.

It has long been known that nervous accidents may be associated with intrauterine manipulations. Most of these accidents occur after intrauterine attempts to produce an abortion. The accidents usually consist of convulsions, generalized or followed by hemiplegia. Death also may follow brisk cervical manipulation. In most cases, accidents which follow cervical trauma and intrauterine operations are blamed on air embolism, but the authors believe this is erroneous. The analogy between accidents after uterine manipulation and pleural puncture leads the authors to study the electro-encephalograms of patients who had intrauterine operations, and they found that there is a uterine reflex just as there is a pleural reflex.

The authors curetted thirteen women without anesthesia and with as little pain as possible. Before the operations the encephalograms were normal, but during manipulation of the cervix the picture changed, and during the actual scraping marked changes were observed. In only two of the thirteen women were the tests negative. Swabbing the uterine cavity produced the same changes as curettement. After the operation the encephalograms rapidly returned to normal. Hence these studies show that intrauterine manipulations, especially at the tubal corners, produce an undeniable cerebral effect, most often unilateral. The cortical hypertony is a true uterine or uterotubal reflex. The authors have shown similar changes during tubal insufflation.

J. P. GREENHILL.

Fernandez, J. H.: Hysterectopexy As Treatment of Complete Genital Prolapse, Obst. y ginec. Latine Am. **3**: 265-270, 1945.

For the treatment of complete prolapse of the uterus the author recommends supravaginal hysterectomy combined with fixation of the cervical stump to the abdominal wall. For this combined operation he proposes the name hysterectopexy. He believes this operation corrects the anatomic relationships, even though the prolapsed tissues are replaced in an exaggerated degree.

J. P. GREENHILL.

Labor: Management, Complications, etc.

de Gouvea, L. R. L.: Considerations of Laceration of the Perineum and Episiotomy, Arch. brasil de méd. **35**: 155-160, 1945.

The author reviews the literature on perineal lacerations and its treatment. He also studied the literature concerning episiotomy, and points out that Ould was the first to employ episiotomy in 1742 and not Michaelis in 1810, as generally believed. de Gouvea discusses the various types of episiotomy and concludes that the mediolateral or diagonal incision is the one which offers the greatest advantages. It does not matter whether the incision is made on the right or the left side. The author prefers the left side. He emphasizes that in order to insure the full benefit of an episiotomy it must be made early but not too early. The repair must be an anatomic one, layer by layer.

J. P. GREENHILL.

de Gouvea, L. R. L.: Transverse Presentation, Arch. brasil de méd. **35**: 239-266, 1945.

The author presents a detailed study of the subject of transverse presentation. At the Carlos Chagas Hospital the incidence of shoulder presentation was 0.64 per cent in single pregnancies, and 5.3 per cent for the second fetus in cases of twin pregnancies.

Among the author's ten personal cases, two were delivered spontaneously, one of which was premature and macerated and was delivered by the Roederer mechanism. The second spontaneously expelled fetus was a 6 to 7 months' abortion which was delivered by the Douglas mechanism. Two babies were delivered by version and extraction. In five cases the fetus was dead, hence decapitation was performed. In one case, rupture of the uterus occurred. Peritonitis followed laparotomy and death resulted.

J. P. GREENHILL.

de Gouvea, L. R. L.: A Case of High Forceps With Inverted Atypical Grasp, An. brasil de ginec. **17:** 1944.

The author used a modification of Llames Massini's inverted grasp with forceps in a case of transverse arrest where he could not rotate the occiput anteriorly either manually or even with the application of Simpson forceps on the fronto-mastoid diameter. The posterior blade of the forceps was first inserted, then the anterior. The head was flexed, the posterior asynclitism was corrected, the head pulled downward and then rotated to an occiput sacral. The forceps were reapplied and the baby delivered without any perineal laceration or injury to the child.

J. P. GREENHILL.

Johansson, H.: Spontaneous Delivery of a Live Full-Term Baby in the Mentoposterior Position, Monatschr. f. Geburtsch. u. Gynäk. **120:** 122-128, 1945.

The author reports a case of spontaneous birth of a full-term living baby in the mentoposterior position. The head was delivered with the frontal suture in the left oblique diameter of the pelvic outlet. The anterior parital prominence therefore was pressed against the lower border of the symphysis and filled the space under the pubic arch. Spontaneous delivery was accomplished by lateral dorsal flexion of the head. There are four similar cases reported in the literature, and in all of these cases the live, mature baby was delivered through an oblique diameter of the pelvis.

J. P. GREENHILL.

Perez G. Lozana, J. L.: One Hundred Cases of Oblique Presentation, Rev. Espãn. de obst. y ginec. **2:** 166-177, 1945.

Among 100 cases of oblique presentations observed at the University of Santiago the causes were as follows: contracted pelvis, 28; pendulous abdomen, 18; multiple pregnancy, 8; fetal gigantism, 4; prematurity, 4; placenta previa, 2; hydrocephalus, 1; arcuate uterus and elderly primipara, 1 each; and undetermined origin, 33. The parity varied from one (18 cases) to 12. Seventeen women were admitted to the hospital with intact membranes, 25 had ruptured membranes with a living fetus, 54 had ruptured membranes and a dead baby, and four women were admitted with rupture of the uterus. Twelve of the 17 women with intact membranes were treated by external version and five by cesarean section. In the second group treatment was chiefly by version under deep anesthesia followed by manual extraction. In the third group 47 were delivered after decapitation, and five by version and extraction. The fetal mortality was 63 per cent and the maternal death rate was 6 per cent.

Necrology

JOHN ALBERTSON SAMPSON, M.D., teacher, author, and a member of the Advisory Editorial Board of the JOURNAL since its founding, died in Albany, December 23, at the age of 75 years. A graduate of Williams College and Johns Hopkins, he came to Albany in 1905, was senior gynecologist at the Albany Hospital since 1937, and Professor of Gynecology at the Albany Medical College. Dr. Sampson was the author of many meticulously written and illustrated papers, dealing principally with research into endometriosis and its associated problems. He was a Fellow and past President of the American Gynecological Society. Born near Troy, New York, he spent his entire professional life in its vicinity, never married, and, aside from his outstanding professional attainments, devoted himself to the raising of trees as a hobby. Quiet, reserved, a scientist in manner and ambition, his researches and attainments were widely recognized.

HOWARD FRANCIS KANE, A.B., M.D., of Washington, D. C., died on July 21, 1946, at his birthplace and final home in Machias, Maine, at the age of 59 years. A graduate of Bowdoin and the George Washington School of Medicine, he became instructor and later Professor of Obstetrics and Gynecology at his Alma Mater, and attending obstetrician at the University, Gallinger, and Garfield Hospitals. During World War I he served with the British Expeditionary Force, was captured by the Germans, interned for six months as a prisoner, received the British Military Cross, and was discharged as a major in the Medical Reserve Corps. In World War II he was made a Commander in the United States Naval Reserve, and was subsequently appointed Chief of the Obstetrical Division of the United States Naval Hospital at San Diego. A member of many medical societies, Diplomate of the Board, an active practitioner in his special field, a foremost teacher, a frequent writer of articles for medical journals, and an excellent speaker, Dr. Kane was closely identified with the development of paraldehyde analgesia in labor and the resuscitation of the newborn.

Correspondence

Adrenal-Like Ovarian Tumor

To the Editor:

I should like to comment on an article written by Dr. Arthur H. Curtis in the July issue of the JOURNAL **52**: 115, 1946, entitled "The Origin of Adrenal-Like Tumor of the Ovary." On page 120 Dr. Curtis writes: "Also, if adrenal rests do give rise to adrenal-like tumors of the ovary, it is strange that adrenal rests are rarely, if ever, demonstrable in the ovary."

I want to take issue with this statement. During my year as resident in pathology in the Department of Obstetrics and Gynecology at Bellevue Hospital, I became interested in fetal ovaries and routinely took sections of the ovary whenever I autopsied a female infant. On one occasion, a section through the hilum of an ovary obtained from a term female stillborn revealed an adrenal rest. Histologically, it resembled the adrenal cortex. I showed it to Dr. William E. Studdiford, Jr., who at that time was director of the department, and he commented that this was not a rare finding, and that he had seen adrenal rests on a number of occasions.

I wonder if anyone else would care to comment on this statement by Dr. Curtis?

GEORGE SPECK, M.D.

AUGUST 7, 1946
2806 SOUTH RANDOLPH STREET
ARLINGTON, VA.

Reply by Dr. Curtis

To the Editor:

Robert Meyer told me that John Miller has made the most exhaustive and dependable survey of the world's literature on ovarian tumors. Miller states (Lubarsch-Henke, VII 3, 752, 1937) that adrenal elements in the ovary itself occur rarely, if ever, with certainty. Usually there is confusion with corpora atretica.

Robert Meyer (Arch. f. Gynäk **145**: 2, 1931) records the accidental finding of an adrenal rest in the cortex of the normal ovary of a four-month fetus; he states, "Most arise in the ligament and include the ovary secondarily."

Saphir (AM. J. OBST. & GYNEC. **37**: 1008, 1939), among three objections to the adrenal rest theory of origin of so-called lutein-cell tumors, emphasizes the rarity of adrenal rests in the ovary.

Walter Schiller has been repeatedly quoted to have found a frequent incidence of adrenal rests in infant ovaries. Dr. Schiller informed me that such is not the case, that he agrees with the belief that adrenal rests in the ovary are exceedingly rare, and that he is in accord with the general belief that nearly all adrenal rests of the genitals are in the broad ligament or hilus of the ovary, rarely, if ever, in the ovary itself. Incidentally, Schiller has seen our so-called adrenal-like tumor of the ovary and agrees with me regarding its origin.

It will be noted that Dr. Speck's tumor was purported to have been present in a section through the hilum of the ovary, not in the ovary itself.

ARTHUR H. CURTIS, M.D.

SEPTEMBER 12, 1946
303 EAST SUPERIOR STREET
CHICAGO, ILL.

Vaginal Lacerations Resulting From Coitus

To the Editor:

Publication of the case report by Dr. Nicholls, which appeared on page 500 of the September, 1946, issue of the JOURNAL, under the title "Rupture of the Posterior Vagina During Normal Coitus," is taken as an indication of the infrequency of this type of accident. I am therefore prompted to communicate my experience with three similar cases, all of which occurred within a recent period of two months.

CASE 1.—I. G., single, white, aged 20 years, was admitted to Roosevelt Hospital at 12:30 A.M. on July 17, 1946, complaining of vaginal bleeding. At 10:00 P.M., two and one-half hours earlier, while having coitus, she experienced a sudden severe pain deep in her vagina "as though something were bursting," promptly began to bleed from the vagina, and soaked 15 perineal pads and two towels prior to admission. Two months previously she had had a spontaneous delivery of a baby weighing 8 pounds 2 ounces, at which time "a number of stitches were taken." This was her first sexual experience since then. On admission, the patient was in shock, with a blood pressure of 80/40, pulse 120, vomiting, and complaining of thirst. A ragged vaginal laceration about 5 cm. in length was found just posterior to, and to the right of, the cervix, extending through the mucosa and underlying fascia, but not involving the peritoneum. A blood transfusion was given and the laceration was repaired with catgut sutures, under pentothal anesthesia. Convalescence and healing were uneventful.

CASE 2.—Just eight days later, on July 25, 1946, another patient, M. W., 28 years of age, single, white, was brought to the accident room three hours after having had intercourse—for the first time, according to the patient. Although not complaining of pain, she began to bleed "in spurts" immediately after coitus, and soaked 10 perineal pads prior to admission. Her blood pressure was 120/80, pulse 100, hemoglobin 10.6 grams. A 3 cm. laceration of the mucosa high in the right vaginal vault was still bleeding. Immediate repair was performed under pentothal anesthesia. Convalescence was uncomplicated.

CASE 3.—This patient, M. B., white, single, aged 24 years, was admitted to the hospital on Sept. 20, 1946, forty minutes after feeling a sudden pain during intercourse. She had had coitus with the same man several times previously. On admission, the patient complained of faintness, thirst, and lower abdominal pain, in addition to the vaginal bleeding, which was rather brisk. Her blood pressure was 135/84, pulse 116, hemoglobin 10.2 grams. A ragged tear, about 4 cm. long, encircled the posterior aspect of the cervix, extending through the vaginal mucosa but not into the cul-de-sac. This rent was repaired under pentothal anesthesia, and the patient left the hospital two days later.

The relative infrequency of lacerations of the vaginal vault among adult women as a result of normal coitus is attested by our hospital records, among which only two similar cases could be found during the past five years.

HAROLD SPEERT, M.D.

THE ROOSEVELT HOSPITAL
NEW YORK CITY
OCT. 12, 1946.

Items

The International Congress of Obstetrics and Gynecology

The Congress will be held in Dublin, Ireland, during the week beginning July 7, 1947, to celebrate the Bicentenary of the Rotunda Hospital. Representatives from all parts of the world have signified their intention to participate in the presentation of an elaborate program which includes addresses and discussions on the history of midwifery, puerperal sepsis, eclampsia, sterility, puerperal mortality, and obstetric shock. Messrs. Thomas Cook and Son, Ltd., are the authorized travel agency and also accept registrations for the Congress. The Honorary Secretary is Mr. G. F. Klingner, Rotunda Hospital, Dublin. The tentative program will be published in the February issue.

The American Board of Obstetrics and Gynecology

Examinations

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 7, 1947.

Arrangements will be made so far as is possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held June 1 to 7, 1947, at Pittsburgh, Pa. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh, Pa.

PAUL TITUS, M.D.

The following physicians are to be included in the list of diplomates certified by the American Board of Obstetrics and Gynecology: Dr. Martin Clyman, 285 Central Park West, New York, N. Y.; Dr. Owen C. Mullaney, 99 Bay State Road, Boston, Mass.

The Central Association of Obstetricians and Gynecologists

The Association offers two annual prizes of one hundred dollars each, one to be awarded for the best investigative, the other for the best clinical presentation in the field of obstetrics and/or gynecology submitted by any accredited physician, research worker, or medical student within the confines of the Association.

For further information apply to Dr. John I. Brewer, Secretary, 104 South Michigan Avenue, Chicago, Ill.

Erratum

In the discussion by Dr. H. B. Matthews on the "Clinical Evaluation of Ectopic Pregnancy" in the October issue of the JOURNAL on page 554, in line 22, the sentence beginning "Nowdays without better equipment," should read "Nowadays with our better equipment." In paragraph five, line 11, instead of "2,000 c.c. of fluid," this should read "2,000 c.c. of blood."

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Norris Vaux, Philadelphia, Pa. *Secretary,* Norman Miller, Ann Arbor, Mich. Annual meeting to be announced.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* A. D. Campbell, Montreal, Quebec. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Earl C. Sage, Omaha, Neb. *Secretary-Treasurer,* John I. Brewer, Chicago, Ill. Annual meeting Louisville, Ky., October 23, 24, and 25, 1947.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* Robert A. Ross, Durham, S. C. *Secretary,* T. J. Williams, University, Va. Annual meeting at the General Oglethorpe Hotel, Savannah, Ga., Feb. 7-8, 1947.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Alice F. Maxwell, San Francisco, Calif. *Secretary,* William Mengert, 2211 Oak Lawn Ave., Dallas, Tex. Annual meeting Atlantic City, June, 1947.

New York Obstetrical Society. (1863) *President,* Harvey B. Matthews. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* F. Sidney Dunn. *Secretary,* James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* Ralph A. Reis. *Secretary,* Herbert E. Schmitz, 25 East Washington St., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* Alexander E. Dunbar. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Carroll J. Fairo. *Secretary,* Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. President, Charles Hunt. *Secretary-Treasurer,* Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* Charles J. Barone. *Secretary,* Eugene A. Conti, 519 North Highland Ave., Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* George Van S. Smith. *Secretary,* Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Goodrich C. Schauffer. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.

Washington Gynecological Society. (1933) *President,* James R. Costello. *Secretary,* Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

New Orleans Obetetrical and Gynecological Society. (1924) *President,* Eugene H. Countiss. *Secretary,* Joseph W. Reddoch, Pere Marquette Bldg., New Orleans, La. Meetings held October, November, January, March, and May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

St. Louis Gynecological Society. (1924) *President,* Otto Krebs. *Secretary,* John E. Hobbs, 630 S. Kingshighway, St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary,* Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Clarence E. Toshach. *Secretary,* John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Obstetricians and Gynecologists. (1938) *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 E. Genesse St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Gerhard Ahnquist. *Secretary,* Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Roland S. Cron. *Secretary,* Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* R. C. Hall. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* S. E. Oglesby. *Secretary,* L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Wynne M. Silbernagel. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.

Naussau Obstetrical Society. (1944) *President,* Austin B. Johnson. *Secretary,* Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Harry Gordon. *Secretary-Treasurer,* J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* H. H. Skinner, Yakima. Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Thomas J. Sims. *Secretary,* LeRoy Goodman, 702 Bryant Bldg., Kansas City Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* George E. Judd. *Secretary,* Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Wallace B. Bradford. *Secretary,* Richard B. Dunn. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* William A. Scott. *Secretary,* James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.

Akron Obstetrical and Gynecological Society. (1946) *President,* H. H. Gibson. *Secretary,* Alven M. Weil, 1030 First Central Tower Bldg., Akron 8, Ohio.

Minnesota Society of Obstetrics and Gynecology. *President,* L. M. Randall. *Secretary,* Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* M. C. Wilson. *Secretary,* George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.